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PERIARTERITIS NODOSA.*

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Up to the present the literature contains the reports of fifty-two cases described as periarteritis nodosa. In addition to these there are probably a number of others which, having been encountered in the early or late process of development, were not recognized as belonging to this peculiar disease of the arteries. On the other hand, some confusion has developed in the use of the term periarteritis or polyarteritis in that a number of authors, not clearly recognizing the individuality of the lesion, described cases of clearly syphilitic origin as types of this condition. We have to-day come to appreciate clearly enough the peculiar clinical and pathological picture in the true forms of periarteritis nodosa to exclude the specific syphilitic nodular arteritis from this group. Hence we are bound to reduce the above number of reported cases to forty-three by omitting the syphilitic cases of Wilks, Pellizari, Baumgarten, Gilbert and Lion, Bruce and Raymond. There can be no hesitation in dropping these cases from discussion, even though the authors define them under the term periarteritis nodosa. Rokitansky's case was the first to be observed, but a clear description of the disease and its pathology was first offered by Kussmaul and Maier in 1866. Their case was clear cut and with it subsequent findings were easily compared. Taking the character of the

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disease as described by Kussmaul and Maier (Case I.) as our guide and dealing only with such in which the diagnosis was fully established by autopsy or microscopical section, there remain forty cases. It is possible that Case II. of Kussmaul and Maier as well as those of Benedict and Sabin may have been of this nature, but as the cases were only clinically observed and the diagnosis rested upon a study of the excised skin nodules, some doubt still remains as to the exact nature of the process.

The mortality as indicated in the study of the forty undoubted cases is one hundred per cent, not including the case reported by Schmorl, dying after an interval of two years of portal thrombosis. This is rather astounding, particularly in view of the fact that the disease has no prominent symptomotology and the apparent progress of the clinical events does not indicate that we are dealing with virulent infection. This high mortality is rather to be viewed in the light that only the fatal cases are properly diagnosed and reported. As the typical lesions are found upon the vessels of internal organs, the skin being involved in only a few cases, no opportunity is given the clinician to analyze the lesions. The clinical diagnosis was made in four cases, one of which died and was verified at autopsy (Schmorl). This rather grave outlook for the proper recognition of periarteritis nodosa must also be viewed from another angle, which is this: Periarteritis nodosa is not a disease entity, but is only a complication of lesions present in an infection which has many other manifestations. As one reviews the well-studied cases there are many points of similarity strongly suggesting a common bacterial infection which, be it through chance or because of a previous preparation of the soil, has led to a localization in and around the arteries. Undoubtedly in many instances a similar localization and infection of milder character involves various systems of the arteries, but in the absence of marked clinical signs or serious pathological change, the cases proceed to recovery without our attention being called to the characteristic lesion. It would appear to us, as we will point out later, that the condition is,

in its mild form, not so uncommon during rheumatic fever and rheumatoid affections.

The term acute nodose periarteritis has been well selected to describe the pathological picture of the cases coming to autopsy. It must be remembered, however, that where recovery takes place and the lesion is examined at a later period the nodose lesion is a fibrous one devoid of all evidence of acute inflammation. The process is one essentially affecting the small arteries, more particularly of the kidney, stomach, mesentery, liver, and heart, occasionally of skin, thyroid, lung, brain, and spleen. The aorta and its main branches show no involvement, in as far as a naked eye recognition of inflammation and degeneration is concerned. Clinically the symptoms vary so greatly that no characteristic picture can be drawn. The most characteristic features are the presence of rheumatoid pains in the muscles and joints, occasional sore throat, some temperature, indefinite colicky pains of the abdomen, leucocytosis and an albuminuria. At times this clinical picture is overshadowed by the presence of cardiac lesions, endocardial, myocardial, or pericardial. For a review of the reported cases up to 1914, I would refer the reader to an excellent article by Lamb. Prior to this, two thorough analyses of the clinical and pathological findings were made by Dickson and Longcope (1908). These previous studies have well outlined the pathological findings, showing a remarkable similarity in the reports based upon the observations of different authors. It might be said that the description of the lesions as found in man has been completely detailed and requires little further addition. It is, however, equally patent that the different attitude of the various observers has led them to place varying importance upon factors and processes so that the final interpretations and conclusions are not in thorough agreement. The part played by syphilis is still debated, while the question of the localization of the initial insult, whether in intima, media, or adventitia, has also led to considerable polemic. More important than these, and yet having received meager attention, is the question why particular

groups or systems of arteries have been picked out by the materies morbi for localization.

We have been interested in diseases of the arteries and have for a long time been on the lookout for a case of periarteritis nodosa. In a series of over three thousand autopsies no case came under our observation until recently when, within four weeks of each other, two came to autopsy. Every advantage was taken of the material and, as neither case had been diagnosed during life, further information was sought for the clinical history to cast as much light as possible upon this indefinite condition. In each instance the patient sought the hospital for aid in conditions not suggesting acute vascular or circulatory disturbances. One would expect that the information obtained from a study of the clinical and pathological findings of the first case would have been an assistance in establishing a proper diagnosis for the second. This, however, was not the case even in the face of the fact that the arteries mainly involved in each were almost identical and that the cause of death, arterial rupture into the peritoneum, was the same. The one striking feature of difference, however, was that there were some subcutaneous nodules in the second case which were not present in the first. The detailed history and findings in those two cases are as follows:

Case I. — E. S. (under the service of Dr. J. I. Johnston), an unmarried woman of 33 years, employed as a music teacher, was admitted to the Mercy Hospital on November 8, 1916, complaining of pain over the abdomen, radiating to the anterior and posterior chest wall. *Past history:* There was nothing important in the history of the family, all of whom are living and well. As a child she had measles, chicken-pox, diphtheria, mumps, and whooping-cough. She has had two attacks of pneumonia, at the ages of 18 and 24, respectively. At the age of 27 she had an attack of typhoid fever. On several different occasions she suffered severe attacks of tonsilitis. In her work as a music teacher, she has had many pupils who at times made her very nervous. Her menstrual history is unimportant. For many years she has suffered constipation. *Present illness:* Three weeks prior to admission she became chilled while out in cold weather and developed severe pain in the back

and loins. With the application of heat, the pain was relieved. A few days later she was again exposed to a rain-storm, so that she was wet from head to foot. On the following day she suffered severe pains in muscles and joints as well as in the region of the stomach. The pains were of a piercing nature. The pains of the abdomen were cramp-like, and of great severity. She was unable to retain food in the stomach and she would have periods of vomiting, unassociated with the taking of food or medicine. The pain in the loins reappeared with greater severity than at the first attack. *Physical examination:* The patient was quite restless as she lay in bed. Examination of the eyes, ears, and nose was negative. The teeth were only in fair condition, showing some pyorrhea. The fauces and throat were quite injected and swollen. There was no glandular enlargement of the neck. Examination of the heart and lungs showed nothing abnormal. The abdomen was rather pendulous; the tissues being well supplied with fat. Tenderness was elicited in the right upper quadrant, and particularly in the region of the gall-bladder. It was thought that a soft mass could be palpated in this area. There was also some tenderness in each flank. The liver and spleen did not appear enlarged.

November 8, 1916: The heart sounds were weak, but no murmurs were found and there was no increase in size. The lungs were negative, the liver not enlarged upward, the spleen not palpable. There was no fluid in the abdomen and the patient was tender all over, but particularly in the right upper quadrant. There had been a history of vomiting and upper abdominal pain.

November 9, 1916: The leucocytic count was 12,000 with 76 per cent polymorphonuclear cells. The patient's scleræ showed slight icterus. There was no further vomiting and the tenderness over the abdomen was more localized in the right upper quadrant, the distention of the abdomen having been relieved by enema.

November 10, 1916: On this day the abdomen was soft and all tenderness except over the gall-bladder was gone. A diagnosis of cholecystitis with acute exacerbation and possibly empyema of that organ was made. The liver dulness extended to the fourth rib and down to the costal margin.

November 12, 1916: All signs pointed to empyema of the gall-bladder, and the opinion of a surgeon was advised. The gall-bladder was palpable and tender; and the patient, while feeling much better and asking for food, showed slightly increased icterus about the scleræ.

November 13, 1916: The patient developed pain and tenderness of a severe type in the right elbow, accompanied by sore throat, but by no apparent swelling. The whole picture, including throat, gall-bladder, and joint, was looked upon as a Streptococcus viridans infection. The proposed consultation with surgeon was then postponed.

November 14, 1916: The patient was improved on this date and little complaint was made of the elbow. No consultation with the surgeon was then held. About 5 P.M. on this date the patient, with very slight complaint of additional pain, went into collapse and died from shock in about fifteen or twenty minutes.

During the period in which the patient was in the Hospital, the temperature was continuously high, ranging from 100° to 103° F. There were no remissions in this temperature, and it never had a septic character.

The urine was repeatedly examined and found to have a high specific gravity, 1,030; was acid, had a moderate amount of albumin and showed the presence of pus cells and granular casts.

The clinical diagnosis was given as acute cholecystitis.

A blood culture taken at the time of death was negative.

Autopsy. — Dr. D. G. Richey (four hours after death): The body was that of a middle-aged, white female, measuring 162 centimeters in length. The body was well developed, slightly jaundiced, and very obese. The scleræ were yellow, the pupils were equal, dilated, and measured 7 millimeters in diameter. There was a slight amount of pyorrhea alveolaris. There was no rigor mortis, and only a slight amount of lividity could be seen over the dependent parts. The thorax was well formed. The abdomen possessed a slight rotundity and was dull on percussion. The external genitalia were normal in appearance. There was no edema of the extremities or scars upon the body.

Thorax: There was no excess fluid in either pleural cavity. Numerous tough fibrous bands of adhesions occurred along the lateral and diaphragmatic surfaces of both lungs. The pericardial sac was quite thin and contained about 20 cubic centimeters of clear straw-colored fluid. On the right side the upper border of the liver extended to the fourth interspace, while the heart had rotated somewhat on its transverse axis and its upper border lay under the second rib in the left parasternal line.

Lungs: The left weighed 340 grams. The surface of the lung was for the most part smooth, except for the fibrous tags of adhesions on the lower lateral and diaphragmatic surfaces. It was of a bluish-gray color and the posterior portion showed some lividity. The lymph nodes at the hilus of the lung were slightly enlarged, but were quite soft and moist and showed no areas of caseation or fibrosis. The lung was fairly anthracotic and crepitated throughout, though in the posterior portion it was somewhat congested. All sections floated in water. The bronchi were reddened and showed a small quantity of frothy yellowish mucus covering the mucosa. The vessels were clear. No evidence of tuberculosis was noted in the organ. The right weighed 225 grams. This organ resembled its fellow in all respects.

Heart: Weight 208 grams. The pericardial surface contained large, irregular masses of fat and the coronary vessels were well marked. The heart muscle was rather flabby and soft. It was dark in color and quite glassy in appearance. The ventricles were empty. The chambers were not dilated. Some fatty plaques could be seen on the aortic and mitral valves. The coronary arteries also showed this condition. Otherwise the heart valves were clear. The F. O. was closed. The A. O. measured 6.8 centimeters, M. O. 8.7, T. O. 9.2, P. O. 6.2, L. V. 2.2 centimeters.

Aorta: The aortic wall was of moderate thickness and quite elastic, and showed a large quantity of fatty streaking of the intima which extended throughout its whole length, greatly predominating along the posterior wall. On the external wall of the aorta, and particularly in the vicinity of the arch and the first part of the descending thoracic, were found a number of small petechial hemorrhages lying in the adventitia and to some extent infiltrating the connective tissue of the vicinity. These hemorrhages formed small blotches, varying from a pinhead to .75 centimeter in diameter. A similar hemorrhagic blotch was also seen at the main stem of the celiac axis. The adventitia of the abdominal aorta was free from this process.

Abdomen: The abdominal wall was very thick, due to a panniculus adiposus measuring 9 centimeters. On exposing the peritoneum, large, irregular, blotchy areas could be seen beneath it. On opening the peritoneum, which was quite thin, the cavity was found virtually filled with dark red blood forming large gummy clots between the intestinal coils. The lower border of the liver was pushed upwards under the ninth rib in the R. N. L. The small intestine was quite flat and there was no sign of peritoneal irritation throughout the abdomen, all surfaces being smooth, moist, and glistening. The great omentum was spread over the greater part of the coils of the intestine. It was very fatty. No enlarged lymph glands could be found in the very adipose mesentery. The diaphragm arched to the second rib on the right side and the third rib on the left side. Over the right lobe and upper surface of the liver, one could see a large oval dark red area, simulating a sub-capsular hemorrhage, which extended to the extreme border of the right lobe. The capsule over the area of hemorrhage was very friable and could be ruptured with ease. No adhesions could be found in the abdomen, except some recent blood clot between the upper surface of the liver and diaphragm.

Stomach: The stomach was not enlarged. The serosal surface was quite smooth and free from adhesions. When opened, the stomach contained a fair amount of thin fluid, which was free from bile. The gastric wall was of normal appearance. The mucosa was fairly thick, indistinctly mammillated and pale. There were no ulcers. The pylorus was healthy.

Intestines: The duodenum, in all its portions, was free from any demonstrable lesion. The bile papilla was rather prominent and presented a slightly reddened appearance. A probe could be easily passed through it, far into the lumen of the common bile duct. The rest of the small intestine showed nothing of particular note. The mucosa was smooth, pale, and pinkish in color. No hyperplasia of Peyer's patches was present. No ulcerations could be made out. The appendix presented a smooth surface and was free from adhesions. It measured 7.8 centimeters in length. The large bowel was similarly healthy throughout its length. The mesentery of the small intestine was very fatty, but showed no change in its vessels or lymphatic structures.

Liver: Weight 2,130 grams; measured 29 x 20 x 8.6 centimeters. The liver was enlarged and felt very soft. On looking down upon the liver in its normal position there was a diffuse red hemorrhagic area under the capsule extending from the costal margin to the diaphragm on its right lateral aspect. The surface of this portion of the liver was irregular and lumpy from coagulated blood. On examination the finger easily passed through the capsule into a mass of blood clot which appeared to lie directly between the capsule and the liver substance. There was no evidence in this hemorrhage of any purulent exudate. The remainder of the superior surface of the liver was smooth, excepting that here and there, particularly in the left lobe, slight, white, fibrous thickenings of the capsule were observed. These fibroses were particularly well marked on the under surface of the left lobe. In places they appeared almost like ridged scarrings. Along the inferior margin of the left lobe there were one or two small fusiform bulgings. These, on section, showed small discrete globular thromboses varying in size from a pea to a bean. The blood in them was clotted and appeared to lie within a vessel wall. In some of these areas there was also some extravasation of blood into the surrounding tissue. The inferior margin of the liver was a little rounded. On removing the liver it was seen that the capsule over the hemorrhagic area on the right lateral surface showed a large tear, from which blood could be expressed. This tear was about 8 centimeters in length. The capsule over this area of hemorrhage could be very easily lifted up and removed. It had been completely separated over almost half of the right lobe by this sub-capsular hemorrhage. The capsule itself was not thickened. The sub-capsular blood clot in places was 1.5 centimeters in thickness. The liver substance appeared intact, showing no evidence of rupture save at one point on the right lateral surface, where the blood clot seemed to be closely adherent and run directly into the liver substance. At this point it appeared that the liver substance was replaced by a mass of blood communicating with the surface. On section into the liver substance at this point, the hemorrhagic area was seen to be pyramidal in shape and extended into the hepatic tissue obliquely in an upward direction. On removal of the gummy blood clot, the wall of the cavity was

dark red, quite friable, and consisted of denuded liver tissue. On section through the liver the tissue had a dull, rather yellow, soft, somewhat mushy character. The general markings of the liver, particularly the lobules, were indistinct. The liver tissue was very easily pitted with the finger. Throughout the liver there were numerous small localized hemorrhages. Some of these hemorrhages were irregular in outline, while others appeared round, and on closer examination were seen to be enclosed in thin vascular walls. Numerous thrombosed vessels were observed. These thromboses were made up of fairly recent red blood clot, but many of them also showed on the side adjacent to the vessel wall a white, partially organized material, which was adherent to the wall. Furthermore, most of the thromboses lay in aneurysmal dilatations of the vessel. In some sacs the wall was very thin and undoubtedly some of the hemorrhage, which appeared devoid of a vascular connection, represented a rupture of these aneurysmal dilatations. The type of structure in which these dilatations occurred was not at first clear. They appeared to be associated with Glisson's capsule. The portal vein was clear in its main stem as well as its branches. The bile ducts also did not show evidence of inflammation. Occasionally, a connection between the hepatic artery and one of the aneurysmal dilatations could be followed out. Some of these dilatations were almost as large as a hazel-nut 1.5 centimeters in diameter. The majority, however, were pea-sized, being 4 to 5 millimeters in diameter. The portal vein at the base of the liver was clear. The main hepatic artery showed a peculiar ridging along its intima, which was firm and had the appearance of an organized exudate. Section of the vessel showed considerable thickening of its wall, made up chiefly of an organizing exudate upon the intima. The common bile duct at the base of the liver was clear. The portal systems throughout the liver substance showed a very prominent Glisson's capsule, and on a little pressure a yellowish bile could be expressed from the duct. Even the smaller hepatic vessels appeared to have thicker walls than normal. There was no bile pigmentation of the liver substance. The left lobe of the liver on account of the prominent Glisson's capsule of the portal system had a moderately fibrosed appearance. There was no bile-staining of the connective tissue, but the portal systems appeared a little glassy and swollen. On numerous sections through the liver it was seen that these aneurysmal sacs filled with blood clot were widely distributed and abundant. There were twenty-eight such dilated sacs of the hepatic artery found in the liver substance.

The gall-bladder was enlarged and presented a fairly smooth surface, with some fine fibrous adhesions bridging between it and the liver. The peritoneal surface was of a dull reddish hue and at one place on the right side in the middle third could be seen a small oval projection which had a blue center with a red areola. This projection felt very firm. On

opening the gall-bladder it was seen to contain about 15 cubic centimeters of a yellow bile. The lining of the gall-bladder was smooth and brown in color. The gall-bladder was thickened by edema, most of which seemed to be in the serosa. The firm mass just described was seen to be a large thrombus which extended from the tip of the gall-bladder to the base. At this point it had been cut across on removing the gall-bladder. The thrombus was red in color, firm, and showed evidence of organization about its edges. It lay in a much dilated vascular channel (cystic artery), which showed a very thin wall. In appearance this vascular channel had exactly the same characters as the aneurysmal sacs seen in the liver. A probe could be passed from one end of the vessel through the open cut end at the base of the gall-bladder. At the tip of the gall-bladder the end of this large dilated channel was seen as a very thick-walled artery, much larger than is usually seen in this situation. At the opposite end, where it had been cut across, the vessel was 2 centimeters in circumference. The cystic duct and the hepatic and common bile ducts appeared healthy. The portal vein showed no thrombosis.

In following the hepatic artery from the hilus into the liver a very remarkable appearance was found. Not only was the vessel of irregular external outline with occasional saccular enlargements involving its whole circumference, but on looking at the inner surface of the vessel the intima appeared curiously scarred and corrugated, frequently showing pits and longitudinal depressions, so that at first sight one was reminded of some of the characteristics of lues. As the vessel extended into the liver occasional stretches of intima were found to be fairly smooth, but then again in the midst of a fairly healthy looking surface would be found an outward pit like a little mouth entering a sac lying outside of the vessel. The appearance of some of these sacs suggested the development of false aneurysms in some situations. Some of these sacs when viewed from the outside had the appearance of a bright red berry attached to the structure of Glisson's capsule. The amount of reaction around the course of the hepatic artery and about the saccular dilatations varied greatly. In some places there was a certain amount of diffuse, pearly, fibrous tissue apparently of recent origin as observed in its succulent character.

Pancreas: Weight 75 grams. The pancreas was 18 cubic centimeters in length. It was of good size and was removed with the duodenum. It had a normal lobulated appearance. On section through the pancreas, the tissue in all portions was yellowish gray, quite firm and healthy. Its ducts and arteries were patent and clear.

Spleen: Weight 130 grams; measured 13.3 x 7.2 x 2.8 centimeters. The organ was of a dark red color and showed several small notches along its convex border. The surface was smooth, finely wrinkled, and glistening to the touch. The splenic substance was soft and mushy.

The cut-surface was moist and the stroma indistinct. The cut edge everted slightly. The Malpighian tufts were recognizable. On scraping the surface large quantities of pulp could be removed. On pressure the structure broke readily, being quite friable.

Left kidney: Weight 141 grams; measured 11.8 x 6.8 x 3.1 centimeters. The capsule peeled quite readily and the surface was left smooth and intact. The surface was a pale pinkish gray in color and showed some slight fissuring. Minute red points could be seen on close examination to stud the renal surface. A few slightly congested blood vessels were noted. On section, the cortex and medulla were well defined. The intermediary zone was slightly darker than either. The cortex was of good thickness, pale pink in color, and many very small red capillaries could be seen arranged in a radial manner. Here, also, the glomeruli appeared as small red pin-point projections. The medulla was pale and presented no striking peculiarities. A large quantity of fat surrounded the renal pelvis.

Right kidney: Weight 135 grams; measured 11.2 x 6.8 x 3 centimeters. The organ was very much like its fellow in every respect.

Adrenals: Weight, 15 grams. The organs were flat and firm. On section the medulla was rather thin. The cortex likewise was thin and showed numerous opaque, yellow, fatty areas. The organs presented a healthy appearance.

Bladder: The bladder was smooth-walled and pale. The mucosa was quite healthy in appearance, though somewhat trabeculated. The openings of the ureters were patent and healthy.

Genitalia: The vagina was small and quite normal. The cervix was of the nulliparous type, being quite small, of normal contour and free from erosions. The uterus was noticeably small in size, measuring 4 x 3 x 1.4 centimeters. The walls were quite thin and the uterine cavity showed nothing of note. The adnexa showed normal structures, save for a few follicular cysts in both ovaries. One hemorrhagic cyst was also noted in each ovary.

Microscopical.

Lung: In some portions the alveolar walls were intensely congested; in other places, the congestion was lacking. Otherwise the tissue was quite healthy looking. The pulmonary vessels showed no evidence of inflammatory change. The adventitial tissues of the vessels showed no evidence of infiltration.

Heart: The muscle fibers appeared fairly healthy. There was some evidence of a granular deposit as found in cloudy swelling, and the nuclear staining was not very distinct. The interstitial tissue, and particularly that in the vicinity of the nutrient vessels, was loose and

somewhat edematous. In a few places this edema was accompanied by a slight amount of lymphocytic infiltration.

Aorta: The general character of the aorta was well preserved. The intima was slightly thickened. The thickening in places had the appearance of an edema with relatively little proliferation, while in other places this loose thickening was accompanied by the presence of a considerable number of large, round cells having endothelial characters. These cells contained fats and lipoids. For the most part these cells lay quite superficially in the loose meshwork of the sub-endothelial layer. Some hyperplasia of the fixed tissues was also evident in the thickened areas, but it was not possible to distinguish a muscular thickening in any coat. Occasionally the intimal reaction was accompanied by an infiltration of lymphocytes which appeared to be making their way from the surface inwards. The media of the aorta was virtually without change. Along the inner surface it was slightly involved in an edema and slight hyaline degeneration. In the adventitia the small blood vessels were distinctly outlined by a perivascular infiltration surrounding the vasa vasorum, so that these small nutrient vessels were clearly outlined from the surrounding loose tissue. This inflammatory response was more prominent in some portions of the aorta than in others. It was particularly marked in a section taken from the abdominal aorta close to the celiac axis. The inflammatory reaction was entirely periarterial, and was found to follow the vasa for short distances into the outer portion of the media. The infiltrating cells were almost entirely composed of lymphocytes, a few plasma cells, and only rarely polymorphonuclear leucocytes. The aortic wall in the vicinity of the vasa showed evidence of injury in the destruction of neighboring elastic fibers.

Liver: The parenchymatous tissue of the liver was altered, but the changes were not uniform throughout the organ. In a number of places necroses were found which involved the greater part of a lobule or several lobules. Some of these necroses showed an infiltration by lymphocytes with very polymorphonuclear leucocytes In other portions of the liver the lobules were quite distinct, though everywhere the liver cells showed an atrophy and degeneration so that the sinuses were more prominent. There was more or less infiltration by lymphocytes in the liver substance. In certain regions the liver lobules were decidedly jumbled as if severely disturbed by nutritional or other change. In these areas the sinuses appeared large, and lymphocytes and blood cells were not uncommonly seen lying between the walls of the sinuses and the liver cells. Various grades of degeneration could be observed in the liver cells. In a portion of liver tissue taken from the area of sub-capsular hemorrhage it was found that the liver tissue was in a much disorganized state, the structure having the appearance of a severe but early necrosis, and the whole being flooded with blood.

The most remarkable change within the liver was found in the portal systems. In these regions all gradations of a non-suppurative inflammation could be found. This inflammatory response often occupied the whole of the portal system so that the artery, vein, and duct were each surrounded by this acute reaction. With this, however, it was remarkable that the duct did not appear to suffer from the presence of the inflammation. In the majority of instances the inflammation was more particularly distributed about the hepatic artery, but the portal vein was not always devoid of a perivascular reaction. Where the inflammation was in its early stages the exudate occupied the adventitial tissues of the hepatic artery, forming a zone or crown of shells in the periphery of the arterial wall. Under these conditions, little change other than an edema was noted. Not uncommonly, however, these milder reactions were also accompanied by a proliferation of fibroblasts which, along with the surrounding edema, gave a very loose appearance to the tissues around the hepatic artery in the portal system. The more severe inflammatory reactions led to a greater non-suppurative inflammatory exudate which encroached more closely upon the muscular portion of the arterial wall. Under these conditions marked degeneration was evident in the muscular wall. In this tissue and without the advance of the inflammatory exudate into the muscle wall itself there was a complete degeneration, whereby the musculature was changed to a hyaline material. This type of degeneration was very striking. Under these conditions the vessel was seen to lie in the center of a non-suppurative inflammation, its muscular walls showing little or no cellular infiltration, and yet giving evidence of extensive damage of the nature of a hyaline or bland necrosis of the muscle. From this stage onward all degrees of distortion and further involvement of the arterial wall was found. Frequently the vessel wall became stretched and thinner. The hyaline band which originally replaced the normal thickening of the arterial coat was stretched and thinned in an irregular manner. The degree to which these small intrahepatic arteries could be stretched without bursting was astounding. All of the arteries were not equally fortunate, rupture having taken place, leading to local hemorrhage and destruction of liver tissue. Although these pouches and dilatations of the hepatic artery were a type of aneurysm, they represented a very acute process in which but little of the arterial coat remained to act as a boundary to the vascular channels.

Where the process of hyaline degeneration was advanced, and particularly in those instances in which the arterial wall had suffered great dilatation, there was an accompanying thrombosis. At times the process led to a complete occlusion of the channel, but more often an opening was still available in the blood clot. The thrombus was of a hyaline type closely adherent to the vessel wall and having irregular patches of

leucocytes and lymphocytes scattered in its substance. The hyaline nature of the thrombus was to a great extent the result of a degeneration of the blood elements within it. The hyaline portion of the thrombus was not rich in fibrin. At times the portal vein was also involved in a perivascular reaction similar to that about the hepatic artery. Processes of degeneration and occasional thrombosis were also seen, but the results of the inflammatory reaction did not bring about the serious consequences with dilatation and rupture that were found in the hepatic artery. In a study of the elastic tissues it was found that the degenerative process accompanying the periarteritis involved not only the musculature, but also these fibers. In the early stages the fibers were found split into several laminæ and frequent interruptions in their course were seen. In the later stages a complete dissolution, in as far at least as the absence of a staining reaction indicated, occurred. Thus the severe involvement of the hepatic artery left no trace of the internal or external system of elastic fibers. In these arteries with advanced degeneration it was difficult to distinguish the line of demarcation between the hyaline thrombi and the hyaline degeneration of the arterial wall. In examining the artery in other sections it was found that during the early stages of the inflammatory process about its wall a reaction of considerable extent involved the media and intima. In some instances the reaction in the intima was unique in that it was out of proportion to the response observed in the media. Under these conditions inflammatory exudate was present in marked quantity in peripheral portions of the artery as well as beneath the endothelium of the intima. In this respect the reaction simulated much that described by McMeans in arteritis occurring in meningitis. The endothelial layer was lifted from its normal position, forming a large bleb containing lymphocytes and some leucocytes as well as evidence of fluid. Between this reaction in the intima and the periarterial inflammatory responses lay the media in which only a few wandering cells were observed. It is true that the degenerative changes occurring in the media were commonly quite out of proportion to the amount of cellular exudate present. In fact it was not uncommonly observed that extensive dissolution of the media of the nature of hyaline degeneration was present in the absence of a definite cellular response. Where the medial degeneration became more advanced there was an exfoliation of the inner loosened intima, laying bare the underlying diseased tissue. It was upon such a denuded area where fibrin thrombosis was prone to develop. The fibrin deposit not only occupied the surface of these tissues, but the threads were found to interlace the meshes of the degenerated media. Associated with these marked reactions of degeneration and inflammation the internal elastic lamina was found to become involved and show tinctorial change. Splitting of this band was common while a change of its composition became apparent in that it no longer

gave the reactions for elastin. Thus the entire vessel wall was involved in grave changes which though commonly beginning in a particular portion of its structure advanced rapidly to include all of its layers. In viewing the gradations of the changes in the vascular wall, one is not surprised that the blood pressure could be properly maintained within the channels. Irregular dilatations were the outcome, the dilatations occurring at the points most severely attacked and least able to contain the internal pressure.

Gall-bladder: Sections were made of the gall-bladder in the vicinity of the thrombosed cystic artery. In the tissue surrounding the gall-bladder there was a considerable edema along with a non-suppurative inflammation localized for the most part about the arteries. Along with the infiltration by lymphocytes there were also many plasma cells and some leucocytes. A proliferation of fibroblasts was also present. In these arteries with the perivascular exudate could be seen a degeneration of the muscular walls similar to that described in the liver. Here also was found a proliferative reaction in the intima accompanied by a lymphocytic infiltration. In the most severely damaged arteries thrombosis was present. The wall of the gall-bladder was in itself but little changed. Small collections of lymphocytes were seen between the muscle bundles. The mucosal surface did not show an acute inflammatory reaction, but the epithelial lining had desquamated.

Pancreas: The tissue was quite normal in appearance. There was no evidence of an inflammatory reaction. The small arteries were free from change. The islands were numerous and appeared healthy.

Spleen: The lymph follicles were very diffuse, so that they were not clearly defined. The pulp substance was much congested. There was no evidence of endothelial proliferation. Some of the blood vessels showed hyaline change of the intima, but there was no evidence of a perivascular inflammation.

Kidney: The tubules of the cortex appeared somewhat irregular on account of degeneration of the lining epithelium and the development of enlarged lamina. The tubular cells were somewhat eroded and there was some débris within the lumen. Some of the epithelial cells had lost their nuclear staining. The glomeruli were large and without evidence of fibrosis. Many of the glomeruli appeared quite cellular, but no definite infiltration by wandering cells was evident. The lining of the capsules and the glomeruli showed some proliferation. The glomeruli were quite compact. The vessels within the kidney were without change.

Mesentery: The sections of the mesentery showed a fairly fatty tissue through which were scattered a fair number of plasma cells and lymphocytes. The tissue appeared loose and edematous. There was no evidence of serious arterial involvement by inflammation. In a few nstances small arterioles were seen around which scattered mononuclear cells were found.

Retroperitoneal gland: The follicles were rather diffuse and appeared loose. The sinuses were dilated and contained many endothelial cells. The appearance of the gland suggested an edema. A fair number of lymphocytes and plasma cells were seen in the stroma surrounding the gland as well as about the vascular channels at the hilus. The blood vessels were not particularly involved.

Right renal artery: The media of the artery showed some fibrosis. The intima was slightly thickened and the elastic lamina reduplicated. In the thickened intima were found some endothelial cells with fat.

Celiac axis: The intima and media of this vessel were healthy looking. In the adventitia there were some scattered lymphocytes and occasional leucocytes. These, however, were not present in large numbers. Occasionally some of the small arteries of the adventitia showed a slight perivascular infiltration. This, too, was not extensive.

Bacteriology: Cultures of the heart's blood showed no growth. Cultures of bile showed Streptococcus mitis and B. proteus vulgaris.

Anatomical diagnosis: Periarteritis nodosa with hemoperitoneum; periarteritis of hepatic artery and artery of gall-bladder with multiple aneurysms; thromboses of hepatic and cystic arteries; rupture of aneurysmal sacs; hemorrhage into liver and peritoneum; jaundice; fatty plaques of mitral valve; fatty change of aortic intima; cloudy swelling of heart and liver; acute splenitis with enlargement; pyorrhea alveolaris.

Notanda: Death resulted from peritoneal hemorrhages arising as a sub-capsular extravasation of blood over the liver. This hemorrhage and others in the liver substance followed rupture of various aneurysms occurring throughout the liver, along the course of the hepatic artery.

Case II. — W. A. W. (under the service of Dr. J. A. Lichty), a man of 53, who was admitted to Mercy Hospital on November 8, 1916, complaining of general weakness and nycturia. For the last year and a half he has not been feeling well, complaining of dyspnea on slight exertion. About two months ago he was exposed to rain and contracted a cold from which he was slow in recovering. *Past history:* At the age of 12 years patient had diphtheria; at 16 he was drawn through a shaft in a mill, having his scalp lacerated over the longitudinal sinus, his chest crushed, and left arm crushed. At the age of 38 he had an attack of typhoid fever (seven weeks); at 39 he had another attack of (?) typhoid fever (six weeks). About nineteen years ago he had a sprained left hip. About eight years ago he had rectal fissures and hemorrhoids. Five years ago he was operated upon for hemorrhoids; he also had his second toe on the right foot removed at the same time (hammer toe). Three years ago patient had an attack of acute rheumatic fever, for which he was in bed three weeks. Right knee is still swollen. *Family history:* Father died of old age, paralytic stroke. Mother died of old age, paralytic

stroke. One brother living and well. One brother died of diphtheria. One brother was killed. Six sisters living and well. *Personal history:* Mail carrier for the last sixteen years. Worked in a steel mill for four years. Traveling salesman for two years. Clerked in a dry goods store for five years. Married. Wife died fourteen years ago of "gastric fever" (?). Two children living and well. Three died at childbirth. Several miscarriages. Patient drinks beer and whiskey, but does not drink enough to become intoxicated. Patient has been a hard and active worker. Exposed to all kinds of weather. Patient smokes. Had gonorrhea. Denies lues.

November 9, 1916: Present condition: Patient lies comfortably in bed. Skin in exposed parts is quite dark in color. There is some cyanosis of the face and particularly of the lips. The small veins of the mucous membranes of the mouth are distinct. The scleræ are slightly yellow. The skin is moist. There are a number of small papillomata in the axilla. There is a large scar just under the right knee, an injury received when a boy. Front of shins shows fine brownish scarring. There are prominent varicose veins on the left side; no edema. Pupils equal and react normally. Tongue shows very marked tremor and is cyanosed and coated; upper teeth are false, lower not very good and show pyorrhea; a good deal of cyanosis of gums.

Lymphatic system: There are no glandular enlargements.

Chest: Expansion fair and equal, tactile and vocal fremitus normal. Chest is resonant in front and in axilla. Posteriorly at both bases a few moist râles were heard, but the lungs were resonant throughout.

Heart: Pulse full, regular, of high tension; some sclerosis of radial artery. Pulsations were visible in neck and along the course of the radial artery. The apex beat was not visible nor palpable. The upper border of the heart lay at the third rib; transverse diameter was 16 centimeters. The left border lay 1.2 centimeters external to the nipple line. Heart sounds well heard. The apex beat was regular. There were no murmurs. At the base the sounds were somewhat distant. Aortic second not accentuated.

Abdomen: Liver extends from the fifth rib to 5 centimeters below costal margin in nipple line. It is palpable and appears smooth. The spleen is not palpable. The abdomen is somewhat prominent, but shows no tenderness or mass.

Muscular system: The left arm is shorter and smaller than the right. This followed an accident when 15 years old. At the present time has perfect movement of shoulder. Right knee shows good movement, but definite creaking can be felt.

Nervous system: There is considerable tremor of body in general. Knee jerks are present.

Urine 1,030, acid, some albumin, leucocytes, and casts. Red blood cells 2,910,000; white blood cells 7,400.

November 20, 1916: Patient has had a slight rise in temperature in the last three days, also increase in pulse rate. Complained of sore throat at the onset. Yesterday bluish raised mottled areas were noted over the legs, thighs, and on the chest wall. These were firm, some were small and nodular, but not very painful. On the anterior surface of the legs they formed large irregular blotches. The general condition remains about the same; cyanosis is not so marked. Red blood cells 2,530,000; white blood cells 13,600.

December 11, 1916: Since the onset of his tonsilitis he has been running a moderate temperature. The nodular, reddish, purpuric areas in the skin still appear about the same. Some have disappeared, leaving only a dull, bluish-brown mottling in the skin with just a suggestion of some induration; other new ones have appeared. These nodules have never been very painful, a point of difference from the usual course seen in rheumatic erythema nodosa. One nodule in the right upper arm became fluctuating and was opened. A thick, gelatinous, brownish material escaped. Cultures from this were negative. He further developed a very husky voice, at times almost imperceptible, was partially conscious most of the time, and showed very marked tremor. The mental condition, in association with cirrhosis of the liver, is somewhat suggestive of Wilson's disease, a degeneration of lenticular nucleus. For the past week the patient has been about the same. The skin condition is not so marked as it was last week or even earlier. White blood cells 21,000. Wassermann reaction ++++ both with lipoid and cholesterin antigen. Blood culture negative.

Temperature: During his stay in the hospital the patient had a variable temperature through the whole course of his illness. This temperature varied between 100° and 103° F. The temperature was of an irregular character, but was never of a septic type.

Death occurred on December 11, 1916.

A blood culture taken at the time of death was negative.

Autopsy: Drs. Maclachlan and Richey (seven hours after death): The body was that of an adult male, past middle life, well developed, but somewhat poorly nourished. There was slight post-mortem rigidity and dependent lividity. The skin, particularly of the face, lips, and mucous membranes, was cyanotic. The lower lips were covered with herpetic eruptions. The pupils were of normal size and equal. A very slight trace of yellow was present in the conjunctivæ. On the chest, anus, abdomen, and thigh were many faint, brown areas of variable size, the remains of the nodular eruptions noticed during life. These pigmented areas were no longer nodular, but still, in some of them, slight induration could be made out, localizing them from the surrounding subcutaneous tissue. On the right upper arm, the scar of a small incision 1 centimeter in length was all that remained of a nodule which in

life was the size of a very large walnut. A number of other nodules of almost equal size were now only represented by faint, brown, flat, pigmented areas in the skin. Over the right chest, at the level of the third and fourth spaces between the nipple and right sternal border, were two nodular areas which on palpation felt about the size of hazel-nuts, but whose skin surfaces showed no change in color. On the left upper arm a very large, bluish, soft nodule, distinctly fluctuating and about the size of a tangerine orange was noted. On section these nodules were found to consist of yellow circumscribed areas of necrosis with central softening. The centers contained a thick, brownish yellow, gelatinous, necrotic material. Running throughout the yellowish necrotic substance of those nodules was much red blood clot. The whole mass presented a soft, friable character, and gave the impression of local necrosis rather than abscess. The section of the skin at a point showing the bluish discoloration presented only a brown, pigmented layer in the superficial, subcutaneous tissue, like the remains of blood effusion. There was no capsule to the nodular area of necrosis, although its outline was quite distinct. The chest was well formed. The abdomen was a little prominent. No scars were present on the penis. A small external hemorrhoid was seen.

Head: The skull cap was thick. The dura was moderately adherent over most of the skull cap. The longitudinal sinus was clear, but it showed very prominent Pacchionian granulations projecting into it. The convolutions of the cortex had a normal appearance. There was no softening to be palpated. A considerable amount of sub-pial edema was present. On section through the brain a very normal looking gray and white matter was observed. The nuclei at the base of the brain showed no degeneration nor hemorrhage. The cerebellum, mid-brain, and medulla presented quite healthy surfaces. The vessels at the base of the brain were not sclerosed to any appreciable degree. The sinuses at the base of the brain were free. The hypophysts were normal and there was no pus in the middle ear.

Thorax: The left pleural sac contained about 200 cubic centimeters of an amber clear fluid. There were no adhesions on either side. The right chest was free from fluid. The pericardial sac contained 100 cubic centimeters of a clear amber fluid. A small milk spot was present over the right auricle.

Lungs: The left weighed 550 grams. The surface of the lung was smooth. The lung was soft and crepitated throughout. On section the cut-surface of the lower lobe was of a reddish-gray color, a little moist, but smooth and glistening. No evidence of consolidation was present. There were no hemorrhages. The bronchi showed congestion of the mucous membranes and considerable thick mucopurulent exudate in the lumen. The peribronchial glands were anthracotic, but there was no sign

of tuberculosis. The right lung weighed 935 grams. It had characters similar to the left lung.

Heart: Weighed 495 grams. The heart was of good size and firm. It contained clotted blood. The chambers were somewhat dilated and the walls were thickened. The myocardium was a little pale, showing a fine yellowish change and in places was almost of the "tabby cat" appearance. The muscle, however, was of firm consistency. The valves at the mitral, pulmonary, and aortic orifices showed slight fibrous thickening along the free margin. The orifices were all relatively enlarged. The F. O. was closed. The coronary arteries showed fatty intimal change with small areas of beginning atheroma in one or two places. There was no narrowing of the lumen of these vessels, in fact many appeared much larger than usual. The A. V. measured 9 centimeters, P. V. 8.5, M. V. 11, T. V. 13, L. V. 2.8, R. V. .9 centimeters.

Aorta: The aorta was thin and elastic throughout its extent; in fact it was somewhat thinner than is usually found. Some small areas of early atheroma were scattered in the descending thoracic and abdominal aorta. The abdominal aorta appeared somewhat wider than usual. In the arch, the aorta was 6.5 centimeters, in the descending thoracic 6 centimeters, and in the abdominal portion 4.5 centimeters in circumference. The iliac arteries were also thin and quite wide. In the abdominal portion there was a single area of calcification. Small areas of pitting with calcification were seen in the right iliac.

Abdomen: The abdominal wall showed a thick fatty layer, and well developed recti muscles. On opening the abdominal cavity about 2 liters of fluid blood escaped. In the upper quadrants of the abdomen about the liver and spleen large masses of recent blood clot could be shelled out. One of these masses, the largest, weighed 450 grams. In the pelvis only fluid blood was present, and this appeared to be mixed with some ascitic fluid, as it was not quite the consistency of pure blood. The great omentum was fatty and had much recent blood clot attached to it in its upper part. It covered most of the coils of the small intestine, which was of normal appearance. The mesentery was intact. No thromboses nor thickenings of mesenteric veins or arteries were made out. The appendix was long, free from adhesions and normal looking. The mesenteric lymph nodes were not enlarged. In the upper abdomen some adhesions of the omentum, fibrous in type, were found attached to the gall-bladder. About the spleen and in the region of the pancreas, in the lesser sac, and retroperitoneally there was a massive and diffuse recent blood clot and hemorrhage. It was impossible to find the ruptured vessel in these tissues. The pancreas could be separated from this mass of hemorrhage only partially and with difficulty. This retroperitoneal hemorrhage extended down to the kidney tissues on both sides.

The diaphragm arched to the third rib on the right and the fifth on the left. The liver did not reach to the costal margin.

Stomach: The stomach was of moderate size. Its lining was smooth and glassy. There were numerous petechial hemorrhages in the mucosa. The lower end of the esophagus did not show prominent veins. The wall of the stomach was not thickened. The pylorus was normal. No perforation nor ulcers were present. The vessels appeared normal.

Intestines: The duodenum showed nothing unusual. There was no blood in this portion of the bowel. The mucous membrane was pale and smooth. In the rest of the S. I. nothing remarkable was noted except two or three small raised areas lying in the sub-mucosa and not eroding the overlying mucosa. They were the size of split peas. They were firm and on section showed a soft yellow tissue with a central mass of blood clot looking like thrombosis of some duration. These bore a resemblance to the nodules of the skin. There was no evidence of inflammatory reaction of the mucosa over them or of the tissue around them. The large bowel throughout its course presented a normal lining and showed no change in its walls.

Liver: Weight 2,700 grams; measured 32 x 22 x 10 centimeters. The organ was very large and well pushed up under the ribs. The organ was surrounded by fluid and clotted blood. The inferior margin was slightly rounded. The capsule was not thickened except the posterior surface of the left lobe, where it was raised into several white arborescent ridges. On section, through these ridges, a bead of yellowish purulent material could be expressed from a central lumen which was surrounded by a thick fibrous wall resembling a vascular channel. In one or two other places similar structures lying in the same relation showed a like purulent fluid. These possibly represented lymph channels, as they were definitely in the capsule. The surface of the liver had a mottled white and yellow appearance. The liver was quite flabby. On section through the liver the tissue cut with increased resistance, and the liver substance felt tough and fibrous. It was pale yellowish gray in color, slightly tinged with bile. There was a diffuse increase in fibrous tissue which involved all parts of the liver equally. The lobules were isolated in round or oval areas by the diffuse glassy connective tissue. No heavy bands of fibrous tissue were seen. The portal channels did not show up prominently, and there was no evidence of special increase of connective tissue about them nor any sign of an acute inflammatory reaction. The portal and hepatic veins appeared quite clear. On several sections through the liver a number of localized round or oval thrombi in vascular channels were noted. In one place the thrombus was clearly seen to be in Glisson's capsule, and the hepatic artery was traced directly to it, showing that it was in the arterial system. These thromboses lay in aneurysmal pouches of the artery and in many the wall of the vessel could be clearly seen. The

thrombi were red and laminated, but some of them showed white peripheries as if early organization were going on. These were firmly attached to the vessel wall. In no part of the liver did we find any evidence of rupture with hemorrhage into the liver tissue. Where the round ligament of the liver entered the liver substance there were marked thrombi, but the round ligament itself was quite normal looking and did not show an involved vessel. In the gastro-hepatic omentum the artery, vein, and duct appear clear. No sign of inflammation of the bile duct could be seen. One thrombus in the liver was traced by section for about 7 centimeters. Its connection with the hepatic artery was demonstrated. The gall-bladder was a little enlarged. It contained about 75 cubic centimeters of a thin yellow bile. The surface of the gall-bladder showed a number of fibrous adhesions which attached it to the omentum. There were also numerous localized nodules in different parts of the gall-bladder which looked, from the outside, like fibrous thickening. The mucosa was smooth and healthy looking. On section through many of these nodules in the wall of the gall-bladder, dilated and thrombosed vessels were found to form the greater part of them. These were quite similar in appearance to the thromboses of the liver and also like those seen in the bowel. Some of the nodules in the gall-bladder wall were larger than others, the largest being the size of a pea. They appeared to lie chiefly in the serosal tissue. No reaction whatever was present in the mucosa. Some of these thickened arteries were traced as they coursed over the surface of the gall-bladder. It was found that these arteries formed chains like a string of beads wherein their walls showed irregular and periodic nodular or fusiform dilatations. The main artery of the gall-bladder formed an irregular mass down one border and it was found that its lumen was obliterated throughout its length by an adherent clot. This thrombus was gray in its periphery and red in the center. The second vertical branch of the cystic artery was not so extensively involved, but was beaded in its outline. In this vessel the dilated sacs alone were thrombosed. At the hilus of the liver, just above the cystic duct and where the hepatic artery breaks up into its several branches, was found an aggregation of dilated and thrombosed vessels. These vessels were ramifying into various directions in the liver. The thromboses had not completely occluded their lumina, but there remained small channels more or less centrally placed. The main hepatic artery lying outside of the liver was not involved in the process. Its inner lining was smooth and there were no sacculations or thromboses. Just as soon, however, as the vessel and its branches became imbedded in the liver substance and in the wall of the gall-bladder, its walls showed inflammatory thickening accompanied by degeneration. No naked eye changes could be observed in the portal and hepatic veins nor in the inferior vena cava as it passed behind the liver.

Pancreas: The organ was enlarged and densely matted down by hemorrhagic fatty tissue which first made its outlines difficult to see. On separating the pancreas, the head was much enlarged, measuring 6 x 4 centimeters. This gradually tapered off toward the tail, which was 5 x 3 centimeters. Under the peritoneal covering the pancreatic tissue looked very pink and there was much diffuse hemorrhage in the pancreatic tissue at the duodenal end. The organ felt firm, but a little softer than the normal pancreas. On section through the head of the pancreas a large dilated aneurysmal pouch the size of a hazel-nut, containing some clotted and fluid blood, was noted. This thrombosed aneurysm was followed and was found to communicate with a small artery lying in the pancreatic tissue at the upper border of the head. This artery appeared to be a branch of the pancreatico-duodenalis. The splenic artery running along the upper border of the pancreas was clear. The greater part of the head of the pancreas had lost its normal appearance. The tissue was dull yellow and necrotic looking with recent hemorrhage perfusing its structure. This necrotic tissue was most evident adjacent to the thrombosed aneurysm. The body and tail of the pancreas were of a pink color and, although none of it was normal looking, appeared glassy, swollen, and degenerated. The lobules were not clear in outline. The whole pancreatic tissue was soft. A few yellow interstitial areas of fat necrosis were also observed in this portion of the pancreas. The head of the pancreas in its necrotic portion had an appearance similar to the large necrotic nodules seen in the skin. The fatty tissue immediately surrounding the pancreas and particularly along its lower border showed numerous hemorrhagic areas. These hemorrhages formed nodular masses at times 1.5 centimeters in diameter. Similar areas of interstitial hemorrhages were observed in the fatty tissues at the tail where the pancreas was in contact with the spleen. No direct communication could be made out between the areas of hemorrhage and the arteries in the tissue. Some of the small arteries had nodules. The splenic artery was followed throughout its length and showed no evidence of thrombosis. At its distal extremity, however, just before it entered the spleen its inner walls were quite corrugated, though intimal hyperplasia could not be made out. The vessel was slightly tortuous and its inner surface somewhat pouched. The splenic vein was normal in appearance.

Spleen: Weight 235 grams; measured 13.5 x 8.5 x 3.5 centimeters. The surface of the spleen on its inner aspect was covered by loose recent blood clot and the omentum and tail of the pancreas were adherent to the hilus. The organ was large and soft with no evidence of a notch on its surface. The capsule showed a few fine tags of fibrous adhesions, but it was not thickened. On section the cut-surface was soft, red, and almost diffluent. The trabeculæ and the follicles were not well seen. The pulp could be easily scraped away with the finger. There was no hemorrhage into the tissues.

Left kidney: Weight 275 grams; measured 14 x 6 x 5 centimeters. The kidney was enlarged and rather soft. The capsule of the kidney was thin and somewhat difficult to peel from the cortex. The surface of the cortex was smooth and of a pale yellowish-red color, showing numerous fine hemorrhages studded over the surface. On section through the kidney, thickening and swelling of the cortex was observed. The cortical tissue was grayish yellow in color. Its markings were not very distinct and it was well studied by tiny red points of hemorrhage. The renal artery and its branches showed no change. A great deal of peripelvic fat was present. The pelvis and ureter had pale, healthy linings and appeared normal. The right kidney weighed 200 grams; measured 13.5 x 7 x 5 centimeters. The kidney was similar to its fellow on the left side. The arteries were without change.

Adrenals: The adrenals were small and covered by a thick layer of fat in which there was a great deal of hemorrhage. The cortex was yellow and well marked, while the medulla was small and somewhat softened.

Bladder: The bladder was of normal size. The lining of the bladder was smooth and pale. The blood vessels appeared normal. The prostate was not enlarged. The cut-surface had a white and fibrous appearance.

Microscopical.

Brain: Section of the brain and meninges showing nothing of note. Sections of the Gasserian ganglion showed a normal structure.

Lung: The lung showed some congestion of its alveolar walls and the presence of a small amount of granular débris in the alveoli. There was no evidence of inflammation and the blood vessels were without change.

Heart: The heart muscle was somewhat loose and the intervening stroma fairly cellular. The musculature showed a considerable amount of fragmentation, but its staining qualities were good. Scattered through the interstitial tissue were occasional small foci of cellular infiltration associated with the small coronary radicals. The infiltration was perivascular and usually quite localized. The larger coronary branches were in no way involved and there was no evidence of true periarteritis nodosa. The cellular aggregations consisted mainly of lymphocytes and resembled mild reactions to infection. In other areas there were small patches of fibrosis in the myocardium. These islands of connective tissue replaced small areas of heart muscle and indicated an old healed inflammatory focus.

Omentum: Sections of the omentum showed the presence of much hemorrhage in the fatty tissues. The main amount of this hemorrhage showed no evidence of inflammatory infiltration. Occasionally, however, small foci of leucocytes and lymphocytes were found in the fatty tissues. The injured blood vessels from which the hemorrhage had arisen were not demonstrated.

Liver: Everywhere the liver showed more or less fibrosis. This fibrosis was present in bands which commonly encircled one or more lobules. These bands were at times quite heavy, but in the majority of instances they were only of fair extent. The fibrosis followed the portal sheathes and did not invade the individual lobules. The liver columns lying close to the bands of fibrous tissue were well preserved and did not appear to be injured by its presence. A few lymphocytes were scattered through this fibrous tissue. Some of the liver cells contained a brown pigment. At times the lobules showed a poor arrangement of the liver columns, appearing somewhat jumbled. Scattered at various intervals the blood vessels in the portal sheathes showed an unusual distortion. Varieties of degeneration and inflammation could be observed similar to that described in the pancreas. The vessels which were particularly involved were the hepatic arteries. These arteries, both large and small, showed periarterial inflammation with hyaline degeneration of the media and aneurysmal dilatation. Laminated thrombi undergoing hyaline degeneration frequently occupied the dilated vessels. Some of the affected arteries were so disorganized that no remains of their walls could be found. Both muscle and elastic fibers suffered severely in the degenerative process so that little remained of their original substance. However, all gradations of this process could be seen in different arteries. In those situations where an artery was severely involved it was found that other vessels, including the veins, also suffered when they were in close proximity within the same portal sheath. Evidences of repair were seen in the granulation tissue surrounding the artery as well as in the organization of the central clot. The main reactions were always of the nature of an acute or sub-acute inflammation in the periarterial tissues, accompanied by a diffuse hyaline degeneration of the media. The inflammatory products did not always enter the medial tissues, but often remained confined to the outer tissues. Likewise, the inflammatory reaction of the intima was variable, sometimes being evidenced in a proliferative response, at other times showing a loosening of its structure accompanied by a cellular infiltration. Where the intima was damaged, and in part desquamated, a thrombus was prone to form. This thrombus, often from the beginning, had a very hyaline character. In viewing the damage upon the various coats of the arterial wall it is not surprising to find extensive pouching of the vessel. In places where the artery had given way, and hemorrhage had occurred into the liver tissue, it was difficult to orient the individual tissues amidst the disorganization. In no place was there evidence of a primary inflammatory process of the liver tissue itself. In each instance it appeared that the arterial affection was quite individual from the functional or structural character of the liver.

Main hepatic artery: The arterial wall itself showed no evidence of

degeneration or acute inflammation. The intimal layer of the artery was somewhat thickened. In the loose tissue surrounding this vessel were seen a number of small arteries which were involved in a mild inflammatory reaction consisting of lymphocytes and plasma cells. In none of these vessels was degeneration of the media observed.

Gall-bladder: A number of sections were made from the gall-bladder and its thickened arteries. The gall-bladder wall showed some edema and infiltration of lymphocytes and plasma cells. Otherwise, the gall-bladder showed little change. The vascular structures, however, formed separate foci around which distinct reactions had occurred. These reactions, with their peripheral inflammatory infiltration and hyaline medial degeneration, were identical with the arteries of the pancreas and liver. There is no necessity for describing these separately. In some of the loose tissue about the gall-bladder the development of new granulation tissue about these arteries was accompanied by a marked infiltration by eosinophiles. Fibroblasts and new capillaries were everywhere abundant. A greater number of small arteries appeared to be involved than was noted in the liver or pancreas.

Pancreas: All gradations from a healthy pancreatic tissue to severe destruction could be observed in a series of sections. Sections obtained from the distal portion of the pancreas showed relatively little change and only occasional vessels were found to be involved in a periarteritis. When, however, sections were obtained from the neighborhood of the head of the pancreas all manner of destruction of tissue was encountered. Wide ranges of complete necrosis devoid of any inflammatory reaction were not infrequent. These necrotic reactions were also associated with blood vessels in which there was interference to the circulation. The arteries within the pancreas showed the most remarkable lesions. In some the adventitia was attacked in a mild inflammatory reaction showing mainly lymphocytes as the cells of infiltration. These lymphocytes were loosely scattered in the surrounding interstitial tissues and did not appear in any way localized to particular tissues or areas. In the earliest vascular changes the inflammatory response preceded the evidence of degeneration in the media. Subsequently, however, a bland hyaline degeneration occupied the entire medial ring wherein the muscle cells appeared to melt down and disappear, save for the homogeneous remnant encircling the lumen. The intima in the early reactions was in no way involved. It was only after marked lesions were found in the adventitia or had advanced into the media that a loosening like a bleb or edema occurred in the intima. This intimal reaction was often accompanied by the infiltration of a few cells. When arterial degenerations had advanced to a degree that the normal elements of the media had been destroyed, a dilatation was prone to occur along the course of the vessel. The extent of the dilatation varied, depending upon the amount

of support in the surrounding structures. Frequently the vessel wall bounding these aneurysmal sacs was entirely lost or at least could not be recognized. The muscle tissue, as we have indicated before, fused into an inert hyaline mass, while the elastic fibers of both the inner and outer coats were completely destroyed and could no longer be demonstrated. At times it was remarkable how an otherwise healthy arterial wall merged abruptly into an aneurysmal sac and was lost in a confused necrotic tissue. This line of demarcation was quite narrow, had a bluish tinge, and was outlined by a zone of leucocytes. On one side of this cellular zone the muscle cells of the media were easily defined, while on the opposite side nothing of them could be recognized. The dilated portion of the artery was filled with a laminated clot, the central portion of which was occupied by a great number of leucocytes. The peripheral portion of the clot was closely adherent to the surrounding tissue, and it was impossible to distinguish the line of demarcation between the hyaline media and the hyaline change of the fibrin clot. The tissues lying at some distance from the involved arteries showed an infiltration by lymphocytes and plasma cells alone. Similar reactions were studied in many vessels of all sizes in the head of the pancreas. The largest of the vessels having thick muscular walls appeared to be involved with as equal frequency as the small ones. Nevertheless, the splenic artery itself along the upper border of the pancreas was not attacked. While this acute reaction with widespread destruction of the arterial wall could be studied in its various stages of advance, it was also interesting to find that many evidences of a reparatory process were also at hand. Arteries were repeatedly found in which repair was present in each of the arterial coats. Of the three coats the intima showed the most active response. Granulation tissue with remnants of lymphocytic infiltration was the common finding in the adventitia. The degenerated media with its irregular bulgings was partly absorbed and replaced by fibrous tissue from the outermost layer. On the other hand, the activity of tissue growth in the intima was most remarkable. A loose fibrous tissue, having the qualities of a granulation tissue with its new-formed capillaries, tended to fill up the lumen of the artery. This organization of the thrombosed vessel was accomplished by proliferation from the adventitia through the media at the time when the intense inflammatory reaction had subsided. Evidences of repair were not alone seen within the arterial wall, but much was also observed in the tissues of the pancreas itself. A granulation tissue was found to occupy areas of pancreas which had previously been involved in acute inflammation and nutritional disturbance. The remarkable feature which struck one in reviewing the pancreatic lesions was the intense destructive character observed in the acute stages wherein the involved tissues were rapidly melted down, as compared with the activity of repair by granulation tissue as soon as the

destructive agents had disappeared. At times this very feature of intense destruction reminded one of the acute necrosis with its sharp line of demarcation, as it is seen in noma.

Spleen: The tissues of the spleen appeared very loose. The Malpighian bodies were small and the pulp substance congested. There were no localized areas of inflammation within the spleen tissue. The arteries were not involved in any unusual process. Through the pulp there was a fair amount of yellow pigment which had been phagocyted by large endothelial cells. In another section a single artery was found within the spleen, which showed some cellular infiltration in its periphery. This infiltration consisted mainly of lymphocytes and plasma cells with a few leucocytes. There was no definite degeneration of the media.

Kidney: The tubules in the cortex showed a considerable amount of change consisting mainly of a granular degeneration and widening of their lumina. Many of these tubules contained a granular débris and the lining cells appeared eroded. At irregular intervals in the cortex there was an increase in the connective tissue. The fibrosis surrounded both tubules and glomeruli and occasionally formed small patches directly beneath the capsule. The glomeruli were large and quite cellular. Occasionally small groups of lymphocytes and leucocytes were found in the glomerular tufts; in other places the glomeruli were adherent to their capsules. Here and there a cellular infiltration was found to surround the capsules in dense collections. These infiltrations often occupied areas of old fibrosis. The arteries showed no evidence of recent attack, but many of them showed thickening of their walls, mainly seen in the presence of a chronic endarteritis. It is evident that the kidney lesion was of two kinds, the one was of old standing with fibrosis; the recent reaction was seen in the granular tubular degeneration and the cellular infiltration which occupied the glomerular tufts and the interstitial tissue.

Adrenal: The cortex of the adrenal appeared rather loose, and the parenchymal cells were poorly staining, and appeared much vacuolated and granular. There was no cellular infiltration within the adrenal substance. On the other hand, the loose tissue surrounding the adrenal was extensively infiltrated with recent blood, the result of a retroperitoneal hemorrhage. Damaged blood vessels could not be found in the nearby tissues.

Subcutaneous tissue: Sections of the subcutaneous tissue showed a very interesting series of reactions. In places, hemorrhage, necrosis, acute inflammation, or granulation tissue were found. These different reactions appeared to be phases of a common injury induced in the tissues. The most marked reaction occurred just above the muscle layer where acute inflammation with a necrosis involved the fatty structures. At times the amount of necrosis appeared out of proportion to the amount of inflammation, suggesting that the necrosis was one of lack of

nutrition. The inflammatory reaction, though accompanied by a considerable number of leucocytes, was not of the purulent variety in that the exudate consisted in so large a measure of lymphocytes, plasma cells, and a great number of endothelial cells. These endothelial cells were often multinucleate, and lay within the pockets of the fat cells. The largest area of necrosis showed a considerable hemorrhage around it, and was probably the result of a vascular lesion in which the structure of the involved artery had been entirely disintegrated. Between the muscular trabeculæ a number of small arteries with infiltration in their outer coats were observed.

Levaditi stain: Specimens of pancreas and liver were stained for spirochetes by the Levaditi method, but none were demonstrated.

Bacteriology: Cultures from a subcutaneous nodule showed Staphylococcus pyogenes aureus and a diphtheroid bacillus. Cultures of heart's blood showed Streptococcus anginosus and Streptococcus salivarius. Cultures of bile showed Staphylococcus pyogenes aureus and Streptococcus anginosus. Cultures from sub-capsular lymph channels of liver showed Staphylococcus pyogenes aureus and Streptococcus anginosus.

Anatomical diagnosis: Periarteritis nodosa with hemoperitoneum; periarteritis of hepatic, cystic, pancreatic, mesenteric arteries and arteries of subcutaneous tissue; aneurysmal dilatations and thrombosis of involved vessels; necrosis of liver, pancreas, skin, and small intestine; chronic sclerotic, aortic, and mitral endocarditia; acute splenitis with enlargement; cirrhosis of liver (syphilis).

Notanda: The immediate cause of death was from hemorrhage into the peritoneum arising in the vessels of the gastro-colic omentum and pancreas. The arterial lesions were typical and easily recognized in the gross. The local distribution of the lesions along the course of the branches of the celiac axis and the superior mesenteric arteries was of interest.

A brief summary of our two cases will bring out the important features more clearly. The first case was a woman of thirty-three years, whose past clinical history gives nothing of importance bearing upon her final illness. Syphilis was not considered as a possible factor, so that unfortunately a Wassermann was not done. Her final illness was of four weeks' duration, beginning with a severe cold following exposure to inclement weather. Muscle and joint pains were prominent, and subsequently these were followed by severe, cramp-like pains in the abdomen. She ran a

continuous temperature over 100° F. There was some leucocytosis and albuminuria and slight icterus. Death occurred suddenly in collapse. The autopsy revealed the typical lesions of periarteritis nodosa with aneurysms and thromboses distributed along the hepatic and cystic arteries. Rupture of one of these hepatic arteries led to extensive hemorrhage about the liver and into the peritoneum. There were no other serious acute lesions nor were there any infectious deposits about the heart.

The second case occurred in a man of fifty-three who previously had suffered considerable illness. He had had acute rheumatic fever. His present illness began after an exposure to rain and cold, from which he was slow in recovering. During his illness he developed tonsilitis, which in a few days was followed by the appearance of bluish nodules in the skin. Dyspnea and cyanosis were evident throughout his illness, apparently associated with an old cardiac lesion. His Wassermann reaction was positive. He had quite a marked anemia, with some leucocytosis. From the time of the onset of his tonsilitis, he ran a continuous though irregular temperature over 100° F. During life one of the skin nodules was removed, but a diagnosis of the arterial lesion could not be made owing to the rather extensive disintegration and hemorrhage which occupied the area excised. Cultures from these nodules were negative, as were also the blood cultures. Clinical manifestations of an intra-abdominal condition were not apparent. The patient died rather unexpectedly, although, during the last week of his illness, he was becoming progressively weaker. His total illness extended over a period of about three months. In this connection, however, it must be remembered that the patient sought the hospital because of cardiac decompensation associated with old heart lesions. On the other hand, the nodules in the skin, and probably also the occurrence of the nodular affection of the internal arteries, developed late in the progress of his disease and while he was in the hospital. It is evident that the patient was primarily suffering from a cardiac lesion of not uncommon type, and that the acute

periarteritis was an associated complication superadded to his other illness. The appearance of the skin nodules took place after an acute recurrent tonsilitis and twenty-four days before his death. The onset of these nodules occurred under the eye of the clinician and the progress of these lesions, as well as the manifestations of the attack upon the internal arteries, was followed during his stay in the ward. At autopsy the involvement of a considerable number of vessels belonging to localized tissues was studied. The distribution was along the ramifications of the celiac axis and mesenteric arteries, as well as the arteries of the skin.

In both of our cases the arterial attack was associated with an acute illness beginning with a cold and tonsilitis and accompanied by a certain degree of muscle and joint soreness. The Wassermann reaction was positive in one, while in the other case syphilis was clinically ruled out.

Previous reports. — As we have indicated above, observations upon periarteritis nodosa have been made upon forty cases. To this number we have added two of our own. It is unnecessary to comment upon the individual findings of previous authors in that many of the reports in the literature contain excellent discussions of them. We particularly refer to the study by Lamb, who gives an excellent review of the thirty-eight cases reported up to the writing of his paper (1914). From this group of thirty-eight cases we have removed two, Case II. of Kussmaul and Maier and the unconfirmed case of Benedict studied in life. With the addition of Lamb's two cases and the subsequent report by Guldner, as well as a case reported by Babes and Mironescu, we have a total of forty. The clinical findings have been well summarized in the report of Lamb, and the difficulty of making a clinical diagnosis during life is indicated in the mistaken conclusions arrived at prior to autopsy. In reviewing the clinical manifestations of the individual cases one is struck by the frequency of common symptoms occurring in all, and at first sight one would be led to believe that there was a certain symptom complex whereby a diagnosis could be established.

The majority of cases occur in males before middle life, who, through a preceding illness, have developed a predisposition for an acute infection not uncommonly beginning with tonsilitis, sore throat, and rheumatoid pains with a final localization of an inflammation upon a distinct group of peripheral arteries. When it is remembered, however, that the entire group of rheumatoid affections are so indefinite in their manifestations, and that the particular tissues and organs suffering the most intense involvement are extremely various, it will be appreciated that in this particular group of lesions the intensity of the symptoms is not constant. Furthermore, if we remember that the localization of this infective process around the arteries is not confined to one vessel or even to one group of vessels, the clinical picture presented in the different cases is quite different. In our own cases we had the opportunity of realizing this fact, particularly when our second case developed the nodular lesions about the arteries six days after we had performed the autopsy upon the first. Even with this evidence in hand we failed to recognize the true character of the disease. On the other hand, the autopsy findings are characteristic and unmistakable.

Syphilis. — From the earliest description of periarteritis nodosa syphilis has been repeatedly discussed as a possible or even probable cause of the lesion. In a number of cases syphilis was found present in other organs, but even in its absence certain authors have compared the character of the inflammatory and the destructive process with syphilitic arteritis. Support was given to the claim of an etiology of syphilis by Kussmaul and Maier, Chvostek and Weichselbaum, Graf, Schmorl and Verse, while its importance as a causative factor is either questioned or wholly denied by the remaining observers. The whole problem of the importance of syphilis in these lesions must be viewed from two angles. Firstly, it is true that in a certain number of cases syphilis was demonstrated in organic lesions by histological examination as well as by the Wassermann reaction (Lamb Case II. and our Case II.). On the other hand, and what is still more

important, there have been a series of cases in which evidence of syphilis has been entirely lacking both clinically and pathologically, and a Wassermann reaction was definitely negative (Lamb Case I., Lewis, Jonas, Veszpremi). This evidence of the absence of syphilis cannot be lightly overlooked, and although it may be claimed that the Wassermann reaction during the acute stages of syphilis is not dependable, yet the lack of any other confirmatory evidence of its presence in these cases is strong argument against the luetic nature of the arterial disease. On the other hand, we are not convinced that, in those seven cases in which syphilis was demonstrated, this disease did not have a predisposing bearing upon the subsequent bacterial invasion of another kind. It is common knowledge that syphilis induces systemic conditions whereby subsequent secondary infections of serious nature may be more readily acquired. We may, however, safely say that the infection of syphilis is not the direct cause of these arterial lesions, but may be only an influence in bringing about subsequent bacteriemias and localized tissue infections. This is furthermore borne out in the absence of true luetic tissue reactions in the involved arteries and in the uniformly negative results reported of tissues stained by the Levaditi method for spirochetes (Beitzke, Verse, Schmidt, Lamb, and both of our cases).

Comparison is made by not a few authors between the similarity of the syphilitic process in arteries and the histological lesions of periarteritis nodosa. This similarity is particularly seen in the manner of attack upon the arterial wall, beginning as an inflammatory process in the adventitia and advancing inwards to the media or even the intima. This inflammatory process is in the main a non-suppurative one, although in the very acute conditions polynuclear leucocytes are not infrequent. Furthermore, there is associated with this inflammation a process of degeneration affecting the media.

While resemblance may be found with syphilitic arteritis the comparison should not be carried too far. It is rather the disposition of the inflammatory exudate than the character

of the cells contained within it, which has given rise to some confusion. It is, however, recognized that syphilis is not the only infection attacking the arterial wall from its outer coats, and that processes of degeneration even resembling the peculiar melting down of tissues may occur in other diseases. We have repeatedly demonstrated the presence of a non-suppurative lesion in the adventitia and media of arteries, particularly the aorta, during systemic infections by the pneumococcus, B. typhosus, and Streptococcus viridans. The presence of these infections leads to a localized inflammatory reaction around the vasa vasorum and apparently occupying the periarterial lymphatic spaces. In the aortic wall the lesions may be followed into the media wherever adequate lymphatics are found about the vasa. It is interesting that under these conditions the area occupied by the non-suppurative inflammation causes a destruction of the surrounding essential elements of the artery. Under ordinary conditions these infiltrations are not extensive, but are sufficiently significant to indicate the course along which bacteria migrate and stimulate tissue reaction. The character of the reaction, being non-suppurative, bears at first glance some resemblance to an early syphilitic process. Our findings have been confirmed by Andrewes, who was able to recover the microörganisms from these foci.

Thus, although various types of bacterial lesions in the arterial wall show a superficial resemblance to those of syphilis, confirmatory evidence must be at hand that treponema pallidum was the exciting cause before arriving at a definite conclusion. This, as we have stated before, is entirely lacking in the study of periarteritis nodosa.

Gross pathology. — It is not our intention to reiterate much of the descriptions which have been so well made by previous authors, save to bring out those points which lead us to believe that the lesion is one induced by sub-acute infection having a peculiar localization dependent upon certain anatomical characters of the arteries. At first sight one is struck by the peculiar feature that periarteritis nodosa

occurs in association with the smaller vessels. This is true only in as far as we recognize periarteritis nodosa as a distinct disease. We would, however, point out that the distribution of the infection is wider than the lesions which attract our eye by gross and often by microscopical means. The arteries most commonly involved, and to which our attention is attracted, are the branches of the celiac axis, the superior mesenteric, the renal, and the coronary arteries of the heart. The distribution upon other arteries, of the skin, lung, brain, epididymis, and adrenal, has been observed in some of the cases. It is interesting that, although the majority of cases have shown lesions which were readily recognized by the naked eye, there have been at least five in which the disease was not discovered until microscopic sections had been made. These were more or less accidental findings of relatively early stages of the arterial process in which the patient had died from causes not directly referable to the vascular involvement. Whether these human cases come under observation with evidence of the early periarterial infiltration or in the later stages when the arterial damage has led to aneurysmal dilatation and thrombosis, is dependent entirely upon the simultaneous involvement and functional incapacity of vital organs. Excluding the cases in which advanced changes have been wrought upon the arteries with death from rupture and hemorrhage, or from necrosis following thrombosis of visceral arteries, death is usually the outcome of severe heart or kidney disease or the peculiar chronic intermittent bacteriemia leading to the so-called "anemic marasmus."

Although the underlying characters of the arterial lesions are fairly constant in the different cases which have been closely analyzed, a considerable variation in the intensity of the inflammatory process and the associated degeneration has been observed. These findings indicate differences in the intensity of the bacterial attack as well as the different stages at which the observations were made. There is every reason to believe that the same infectious agent acting over similar periods of time will produce, when the tissues are

equally susceptible, fairly constant injuries to the arterial wall. Thus, when the damage has been sufficient to produce arterial weakening, dilatation results, which we are justified in comparing with the so-called mycotic aneurysms. This interpretation is borne out in the further analysis of the lesions. Eppinger has classified the manner in which acute mycoses may become localized in certain arteries or upon particular portions of the arterial wall. Some of these begin by direct extension of the infectious process from lesions upon heart valves. These begin in the intima and extend outwardly. In another group intimal lesions are likewise primary, having their origin from infected emboli locating at the bifurcation of vessels. Similarly, infections of the arterial wall arise in the outermost coats of the arteries from neighboring suppurative lesions bringing about focal destruction of tissues, with the erosion of media and eventual saccular aneurysms and rupture. Finally, a fourth type is indicated in which the distribution of the infectious agent takes place by means of the vasa vasorum from a distant focus. Under these conditions several foci may become implanted in the wall of the artery and simultaneously progress to a destructive lesion sufficient to produce multiple mycotic aneurysms. It is with this last group that our interest chiefly centers. Whereas the discussion in regard to this type of mycotic aneurysm has constantly brought to the fore the importance of the vasa vasorum in the process of distribution, it is found that these minute vascular channels play only a temporary part in the progress of the lesion. If, under certain circumstances, bacteria are brought by way of the vasa vasorum to the artery they soon make their way into the surrounding lymphatics and then continue their migration and tissue destruction from these sites. This gives rise to a true perivascular reaction about the vasa, and has a harmful influence upon the larger artery. We are not convinced that the initial infection about the vasa is always implanted by the arterial stream of the nutrient vessels. It seems more probable, and this we have been able to follow in a number of cases of pneumonia, that the infection has

from its beginning been one of the lymphatic structures and that its distribution has been of the nature of a lymphangitis. Thus, within the thorax with its rich lymphatic centers in the tissues of the mediastinum, infection radiates along the course of the lymphatic channels and involves those tissues which are in closest proximity or are most readily reached by the distribution of the lymph channels. We find that the majority of acute arterial mycoses are localized in the same situations in which the syphilitic virus is found. The common acute mycotic aneurysm of the aorta lies in the ascending limb of this vessel, and when we study these lesions in their various stages of development we find that they begin in the outer loose tissues of the adventitia and extend into the arterial wall in the vicinity of the nutrient vessels. This portion of the aorta has a rich lymph supply, and is in direct communication with the lymph nodes of the anterior mediastinum. Next in frequency mycotic aneurysms are found upon the transverse and descending arch. In the abdomen the localization of infectious processes upon the aorta is in the vicinity of the root of the celiac axis, in which position an unusual cluster of lymph nodes and channels surrounds the large vessel. Thus in the study of the distribution of mycotic aneurysms of the aorta, we must bear in mind the richness and complexity of the lymphatic bed of the part. Furthermore, it would not be amiss to include the cases of multiple mycotic aneurysms of the aorta in the consideration of periarteritis nodosa, remembering always that, because of the difference in the structure and function of this large vessel, the lesions have some features distinct unto themselves, and, therefore, present a picture not directly comparable to those of the smaller arteries.

The importance of the perivascular lymphatics is not sufficiently appreciated by most investigators when considering the mode of distribution of bacteria in and about the vascular tissues. Every one who is familiar with the pathology of inflammatory reactions in the human subject has had his attention attracted to the presence of perivascular exudate

in the periphery of the focal inflammation. It is not uncommon to observe the advance of infection and inflammation in tissues surrounding the small arteries of the mesentery of the appendix during acute inflammatory lesions of the appendix. It is probable that the thromboses so commonly occurring in the vessels of these outlying tissues have their cause in the damage induced through infections of the arterial coat arising from the perivascular involvement. The same perivascular responses are also to be observed in the Fallopian tubes, the broad ligament, the umbilical cord, and elsewhere. In this respect it is interesting to note that Cullen reports a case which might be regarded as periarteritis nodosa of the umbilical vessels. He quotes Runge as saying "that where infection of the umbilical vessels exists the disease first starts in the perivascular connective tissue. . . . Often the process extends to the adventitia and the vessel itself is involved. The inflammatory infiltration of the vessel wall causes a paresis of the muscularis or dilatation of the vessels or gives rise to a thrombus which soon breaks down." This migration of the inflammatory exudate is not a condition which per se tends to follow the artery, but which, because of the lymphatics, is the line of least resistance in this process. This is true not only of infections of the suppurative type, but also of the non-suppurative lesions. Of the latter it has always been frequently demonstrated that the infections associated with acute rheumatic fever and the various rheumatoid processes are for the most part periarterial in their distribution. The focal inflammatory deposits that are so constantly found in the myocardium in rheumatism are excellent examples illustrating the localization in the lymphatic spaces and channels of the nutrient vessels. Thus we are led to believe, and we have further demonstrated in experiment, that periarteritis nodosa differs from the common periarterial inflammations only in the peculiar manner of damage to the arterial wall. The distribution and the progress of the disease along particular branches of arteries is not unique for this lesion which has received a special name.

Microscopical analysis. — Here again we need not review in detail the observations by others nor enter into a lengthy description of the lesions, save in as far as they present characters differentiating them from periarteritis so commonly met with. In periarteritis nodosa the inflammatory reaction is in the main a non-suppurative one, but one which in the same individual may show foci of more intense inflammatory reaction and the presence of large numbers of leucocytes. In the later stages of the lesions these leucocytes are often eosinophiles. The presence of large numbers of the neutrophilic leucocytes is an indication of a heavier focal infection of the same microörganism, or a response following upon tissue degeneration and necrosis not unlike the leucocytic involvement of typhoidal focal necrosis of the liver. In the early stages of the periarterial attack the infection appears to lie in the tissues outside of the artery, and only at sporadic intervals does the inflammatory exudate involve the adventitia. In many positions the artery shows no further involvement and does not suffer damage to its walls proper. These areas constitute the portions intervening between nodules and aneurysmal dilatations. In the region of the nodules the inflammatory processes proceed into the arterial tissues proper, where products of degeneration are soon observed in the muscular portion of the media. Degeneration of the middle coat may proceed to great lengths without the presence of exudate, but it is not uncommon to find more or less cellular infiltration accompanying the reaction. The medial degeneration is hyaline in character and appears to result from both toxic and nutritional disturbances. That it is not alone toxic is often observed in the localized position of the degeneration, where the entire circumference of the artery is equally involved in inflammatory response. Under these conditions the nutrient vessels as well as the lymphatic drainage are seriously damaged or occluded and the tissues dependent upon their efficiency suffer complete asphyxia. We have in several instances observed the presence of hyaline medial degeneration in the arterial wall beyond the acute inflammatory response, in which it was found that the vasa

supplying wide stretches of the artery were involved. It is probable that the diffusible toxins of the infection play a part in bringing about the characteristic degeneration. Whether interference with the circulation in the vasa vasorum alone can bring about the widespread and peculiar medial degeneration is not clear, but we rather doubt it.

For the most part the presence of nodules along the course of an artery indicates aneurysms. On the other hand, however, smaller nodules may be recognized which, on histological examination, show no aneurysmal dilatation of the vessel, but a marked inflammatory infiltration with edema and granulation tissue. Aneurysms may be observed in all stages of development as well as in a variety of types. At times the dilatation is fusiform or spindle-shaped, there being a uniform distention of the arterial wall in its entire circumference. In these specimens the artery is equally involved in all its coats and on every side. Small saccular aneurysms are also encountered in which the bulging is more pronounced in one direction, owing to the more marked attack at one point than another. Again we have observed the development of a false aneurysm where the tissue of the artery has given way with rupture and the development of a blood sac in tissues outside of the artery and not bounded by its coats. A common and almost constant characteristic of these aneurysms is thrombosis, occupying not only the sac, but also much of the natural arterial lumen. This thrombosis differs considerably from that observed in the more common aneurysms. Under ordinary conditions an aneurysm develops through the dilatation of an artery in which the inner coats, though modified in their architectural arrangement, still remain intact. The thrombus which develops within such an endothelial-lined sac is laminated and undergoes change slowly, as the granulation tissue replaces it. The thrombus in periarteritis nodosa might more appropriately be spoken of as an acute thrombus, developing not only in consequence of the slowing of the blood current within the sac, but more particularly because of peculiar changes in the arterial wall with which it is in

contact. It must be remembered that the aneurysm in periarteritis nodosa is an acute one, becoming established within a few weeks. The arterial wall suffers an acute degeneration and inflammation in which its wall from adventitia to intima is involved. The endothelial lining is either destroyed or exfoliated, so that the underlying damaged structures are in direct contact with the blood stream. It is upon these tissues in a state of necrosis that the blood rapidly coagulates without showing the laminated arrangement so commonly present in thrombi of slower production. It is furthermore observed that the fibrin coagulum is firmly attached to the arterial wall and even appears to suffuse the tissues to some depth. In this position the fibrin becomes altered and assumes a bland hyaline appearance, so that it is indistinguishable from the similar degeneration of the musculature of the media. Thus in the aneurysmal sacs containing thrombus it is impossible to recognize demarcation between the original arterial wall and the hyaline clot within it. It would appear that those substances which act upon the musculature of the media and convert it to a homogeneous product of degeneration have a similar effect upon the constituents of blood clot. When thrombosis has once begun it rapidly progresses to the occlusion of the entire artery.

It is well to call attention again to the finding in microscopical studies of inflammation about arteries, that inflammatory processes with marked cellular exudate follow the course of the lymphatics in the outer arterial wall and are common to a variety of infections. The inflammatory reaction showing a non-suppurative exudate and having a predilection for the adventitia and periarterium is most commonly associated with the bacteria belonging to the Streptococcus viridans group. Systemic infections by these microörganisms regularly involve groups of arteries in one or more organs. The arteries of the heart, kidneys, meninges, muscles, and subcutaneous tissues are so frequently the points of localization of this infection that, depending upon the persistence of the attacking microörganism and the progressive damage done in local areas, our attention is

particularly attracted to one of these tissues. The bearing of these findings under conditions other than periarteritis nodosa is more clearly brought out in an analysis of the bacteriology which has been made upon some of the reported cases.

Bacteriology. — Several cultures were made from different fluids in each of our cases. In Case I. no blood culture was obtained during life, but a culture was taken from the arm vein within a few minutes after death. No growth was obtained. At autopsy a culture made from the heart's blood gave negative results, but a culture of the bile from the gall-bladder showed the presence of Streptococcus mitis and B. proteus vulgaris. In Case II. a blood culture obtained during life was negative as was also the culture of the necrotic material obtained by excision of one of the skin nodules. Another blood culture made immediately after death was negative. At autopsy a culture from a nodule over the pectoral muscles gave Staphylococcus pyogenes aureus and a diphtheroid bacillus; heart's blood gave Streptococcus anginosus and Streptococcus salivarius; bile gave Staphylococcus pyogenes aureus; nodule of liver gave Staphylococcus pyogenes aureus and Streptococcus anginosus; lymphatics of capsule of liver gave Staphylococcus pyogenes aureus and Streptococcus anginosus.

With these findings it is difficult at first sight to conclude which, if any, of the organisms played the important part in the inflammatory process of the arteries. The presence of the staphylococcus and the diphtheroid bacillus in the softened nodule beneath the skin is a finding which does not particularly attract our attention. The presence of these microörganisms in lesions of these tissues is a not uncommon finding. On the other hand, the presence of streptococci in different regions as well as the rather wide dissemination of the staphylococcus offer points difficult of interpretation. We are, of course, aware that microörganisms invade widely the dead body and continue to spread with the increase in time after death. It is also important to remember that an

agonal invasion not uncommonly takes place by bacteria having no direct relation to the disease present in life. In our two cases, however, such an agonal invasion was not demonstrated. On the other hand, it is a not uncommon finding to demonstrate bacteria in local foci in the absence of them in distant body fluids. It is possible that infective agents localized in and about the liver do not make their appearance as a bacteriemia, but only after death find opportunity to advance by growth into neighboring organs. Thus the heart blood may easily show the presence of infection several hours after death when bacteria have grown to it in the blood medium from a neighboring organ like the liver. It is probable, however, that the variety of organisms isolated in Case II. was not present at the onset of the arterial affection, but that some of them were true secondary invaders attacking a damaged tissue.

Relatively few of the cases of periarteritis nodosa have had a bacteriological investigation. It is interesting, however, that of seven previous reports one was negative (Veszpremi); five showed the presence of some type of streptococcus (Datnowski, Jonas, Beattie and Douglas, Lamb Cases I. and II.); two showed the presence of Staphylococcus aureus (Oberndorfer and Lamb Case II.); two showed the presence of B. coli (Lamb Cases I. and II.); one showed the presence of B. influenzæ (Jonas). Besides this we find that Longcope and Babes and Mironescu observed the presence of streptococci in sections of the arterial lesions. In taking all of the cases (nine including our own) in which cultures have been made, we find that seven gave streptococci either alone or mixed with other bacteria. In the absence of cultural differentiation it is impossible to say what types of streptococci were most commonly found. It is probable that the streptococcus isolated in Lamb's second case was a Streptococcus mitis. From our own findings we are led to believe that the infecting agent is not always the same, and that, therefore, we are in no way dealing with a disease entity. The finding in both of our cases of a streptococcus of the viridans group as well as of another type belonging to the

hemolytic streptococci suggests strongly that this variety of bacteria plays an important part in the development of the peculiar arterial lesions. As we have already pointed out, a number of these cases present a previous history which we are wont to associate with infections by this group of micro-organisms; while furthermore, not a few clinical manifestations which are so commonly seen during infections by the viridans group were observed in these patients.

Respecting the importance of the syphilitic virus we are inclined to agree with Lamb and others that it plays only a secondary part. It is possible, as we have intimated above, that the systemic influence of syphilis permits a secondary invasion more ready access. It is of importance that these lesions of periarteritis nodosa which are met with in their acute process have never shown the presence of the spirochete. It is furthermore important that nodular lesions of arteries similar to those in man have been observed in deer (Lupke and Jaeger), pig (Joest), and calf (Guldner).

Animal experiments. — Although in a number of cases bacteria have been isolated from the lesions, Lamb alone has attempted to reproduce the process in animals. He inoculated a guinea-pig, a rabbit, and a monkey with the Streptococcus viridans which was obtained in his second case. These animals showed no manifestations following the injections, and when killed two months later showed neither gross nor microscopical lesions. Another rabbit inoculated with a large dose of the same microörganism died in eighteen hours without showing anything definite.

We have carried out a series of animal experiments using the three types of streptococcus which were isolated from our cases. Rabbits were used in all experiments. Five animals were inoculated with Streptococcus mitis, two with Streptococcus salivarius, and five with Streptococcus anginosus. The manner of inoculation was the same for all animals. The method of the experiment attempted to place the microörganisms into the periarterial lymphatic spaces so that the inflammatory reaction would, from the

beginning, be localized about the arteries, and would have an opportunity of progressing in these channels along the course of the artery and its branches. For this purpose two regions in particular were selected for the points of injection; the regions being selected because of the rich lymphatic supply about the neighboring arteries. One of these was in the abdomen, the other in the thorax. The abdominal inoculation was made, following a laparotomy for exposure, into the periarterial tissues of the celiac artery just after it was given off from the aorta. At times the tissues about the mesenteric artery were also infected. The inoculation was made by syringe with a fine needle. The cultures were usually concentrated by centrifugalization so that only a small bulk was necessary to be introduced. The laparotomy wound was then carefully closed, care being taken to avoid infection of the peritoneum. Only one animal developed peritonitis. The second region chosen for inoculation was the anterior mediastinum of the thorax. It was found, after several trials upon dead animals, that an inoculation could be made into the loose mediastinal tissues, rich in lymphatics, by introducing the hypodermic needle from above downwards behind the sternum. It was found not difficult to reach a position just below the aortic arch. The results of our experiments will be given only in summary, reserving the details for a later and more extensive analysis.

The Streptococcus anginosus was found to have an unusual pathogenicity for rabbits, so that the dose had to be reduced much below that given for the Streptococcus mitis and Streptococcus salivarius. Out of the five animals inoculated with Streptococcus anginosus, four died in less than twenty-four hours, the fifth was killed at the end of eleven days. The marked feature resulting from the inoculation of Streptococcus anginosus was the local necrosis of tissue surrounded by an inflammatory zone of limited extent. Even in the animals dying in less than twenty-four hours, the tissue necrosis was quite marked. The inflammatory reaction was accompanied by much edema with widening of the tissue

spaces and an infiltration by varying quantities of inflammatory cells. The migration of the inflammatory reaction could, at times, be followed for a considerable distance along the blood vessels. At times a sub-acute periarteritis appeared along the hepatic artery in the liver or along the splenic or the branches into the pancreas. Non-inflammatory necroses were found in various portions of the pancreas. Similar reactions were also observed in the mediastinum, but here it was more difficult to follow the inflammation along the individual vessels. Occasionally the reaction followed the vasa vasorum on to the aortic wall, but more definite responses were observed about the small arteries of the mediastinum.

Somewhat better results were obtained with the use of Streptococcus mitis and Streptococcus salivarius. The animals were examined after a period of from two to eleven days following the inoculation. In no instance was a true periarteritis nodosa obtained. Nevertheless, very interesting lesions, in many respects simulating the early responses of periarteritis nodosa, were obtained. It was found that, by the method employed for infecting the arteries, it was not difficult to obtain a periarteritis of various grades of intensity. Where larger doses of bacteria were inoculated at a single point, a reaction by polymorphonuclear leucocytes was the result. With smaller doses and in regions at some distance from the point of inoculation the cellular reaction was mainly composed of lymphocytes and plasma cells with relatively few leucocytes. The majority of these reactions were truly perivascular, as are those so often found in many human infections of various tissues. These perivascular reactions lie outside of the arterial wall and occupy the lymphatic spaces which follow the course of these vessels. On the other hand, we also obtained in these experiments a type of perivascular reaction, which at different intervals along the route of the artery advanced towards the arterial wall proper, leading to an inflammatory zone in the adventitia as well as in portions of the media. In two instances arteries were observed in which a hyaline change occurred in the tissues

of the adventitia and outer portion of the media. In one other instance we obtained a complete hyaline destruction of the media without any evidence of inflammatory cells occupying the arterial wall proper. The only inflammation in this latter instance was found in the perivascular tissues. In none of the arteries had sufficient weakening of the walls occurred to permit of the characteristic dilatation and thrombosis. Although our experiments have not been successful in reproducing the lesions, we are sufficiently encouraged to continue the methods used in these experiments for the reproduction of the lesions. One of the difficulties which we have found hard to control is the proper gauging of the dose to be inoculated when the virulence of the microörganisms changes so markedly on artificial media. It is possible also that the rabbit is an unfavorable animal for carrying out these experiments, and it may be found that the reproduction of the particular injuries can be more readily accomplished in other animals.

CONCLUSIONS.

Periarteritis nodosa, a disease process of man and animals, is of rare occurrence. Records of forty human cases have been found in the literature, to which we have added two of our own.

The lesions are distributed along one or more arteries and their branches. The distribution is by way of the periarterial lymphatics.

The process is an inflammatory one, beginning in the outer portion of the artery and accompanied by a hyaline degeneration of the media. The intima is only secondarily involved, as it is disturbed by inflammatory or degenerative conditions in the outer arterial coats.

Secondary aneurysms with rupture are not uncommon. Thrombosis of the involved arteries may lead to nutritional disturbances of organs and tissues supplied by the vessels.

Syphilis, although present in a number of cases, is not the exciting factor, but may play a rôle in inducing greater susceptibility of tissues.

The most important agent which has been found as the probable cause of the lesion is the group of streptococci. It is probable that no particular member of the streptococcus group is alone responsible for the arterial lesions.

Animal experiments have shown that various types of streptococci may induce individual reactions similar to those observed in periarteritis nodosa, but up to the present no characteristic damage has been produced upon the arterial wall whereby aneurysm, thrombosis, and rupture have presented the picture seen in the human form of periarteritis nodosa.

[I am much indebted to Dr. H. H. Permar for the illustrations which accompany this paper.]

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(A full review of the literature is contained in the articles by Lamb and by Dickson.)

EXPLANATION OF PLATES I. AND II.

PLATE I., FIG. 1. — Periarteritis nodosa in wall of gall-bladder. (Case II.)

FIG. 2. — Periarteritis nodosa of hepatic arteries. (Case II.)

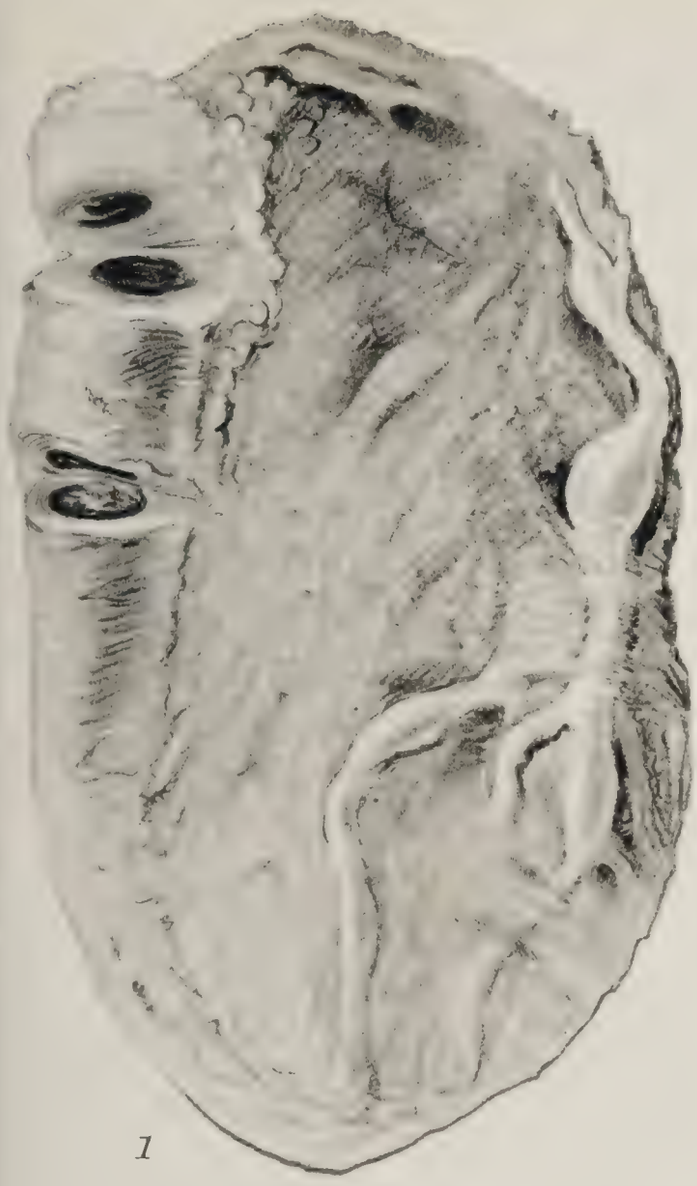
FIG. 3. — Acute degeneration of hepatic artery with aneurysm and thrombosis. (Case I.)

FIG. 4.— Acute periarterial inflammation with hyaline degeneration of media. (Case I.)

PLATE II., FIG. 5. — Acute non-suppurative periarteritis with advancing hyaline degeneration of the media. (Case II.)

FIG. 6. — Experimental periarteritis with secondary mesarteritis and endarteritis.

FIG. 7. — Experimental periarteritis with early hyaline degeneration of outer media.



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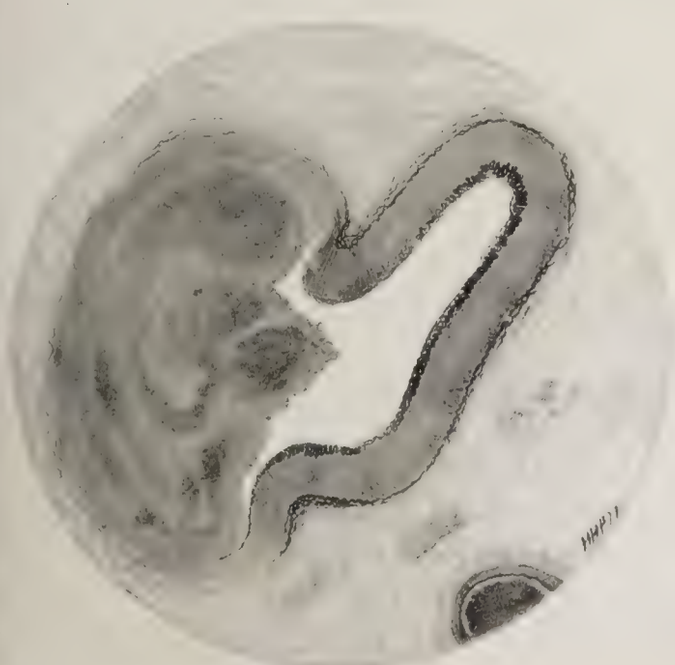

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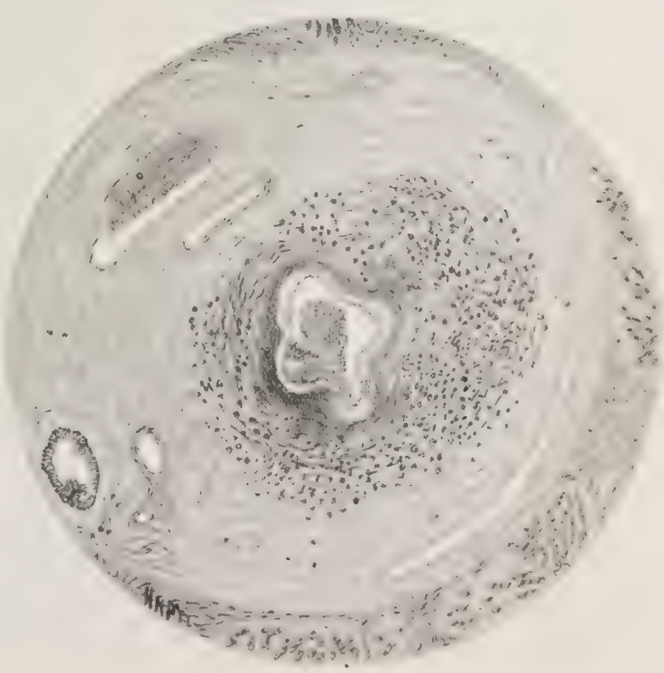

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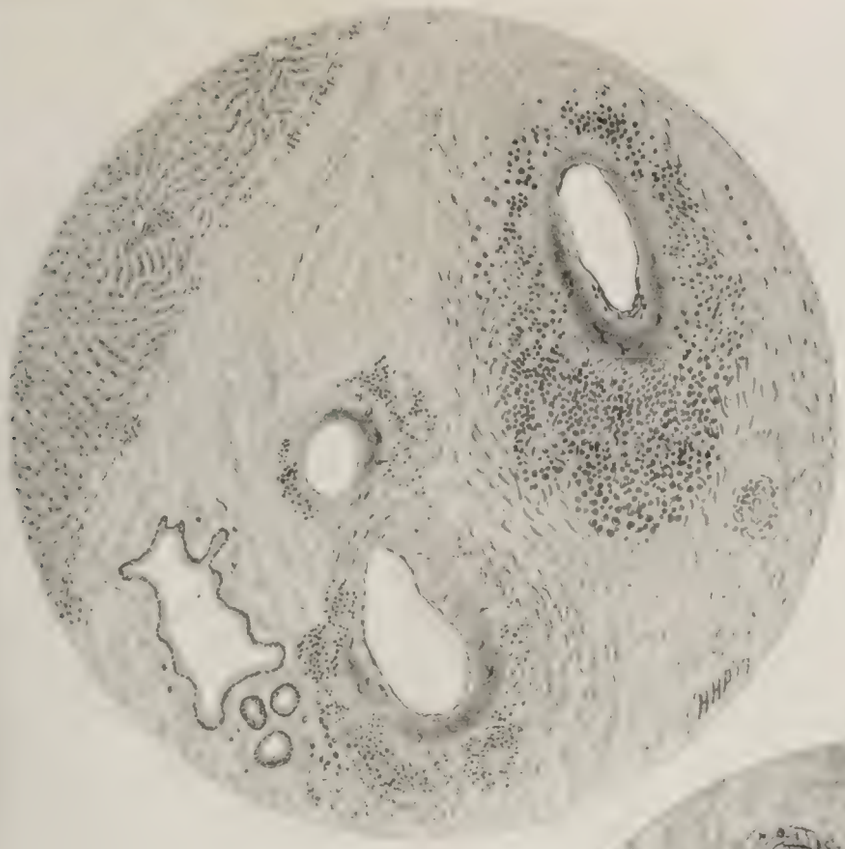

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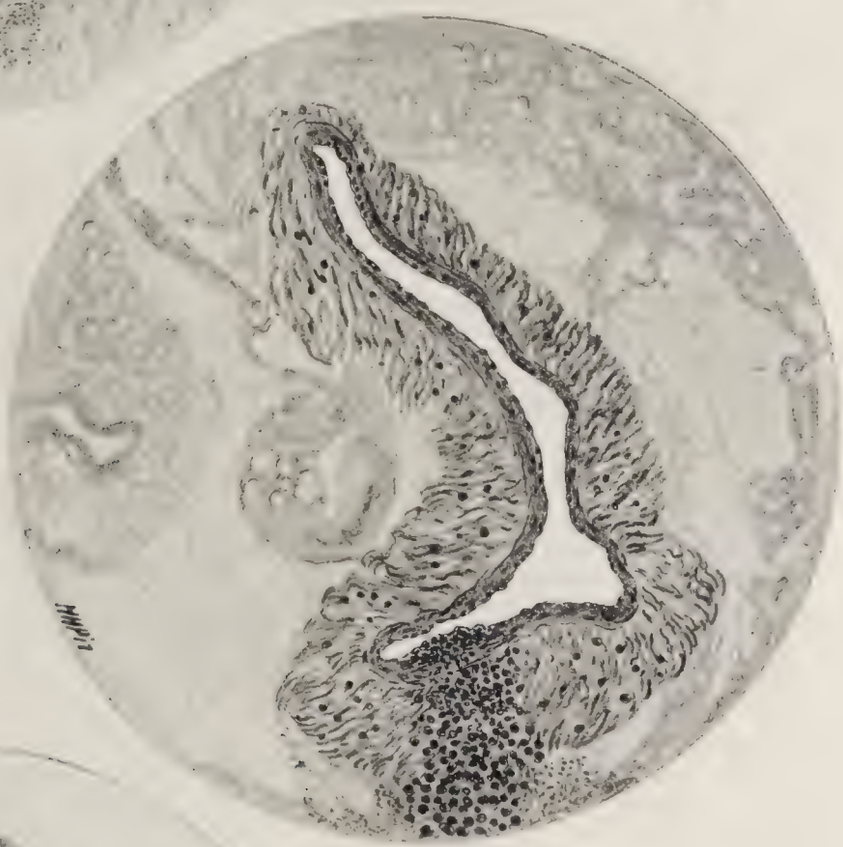

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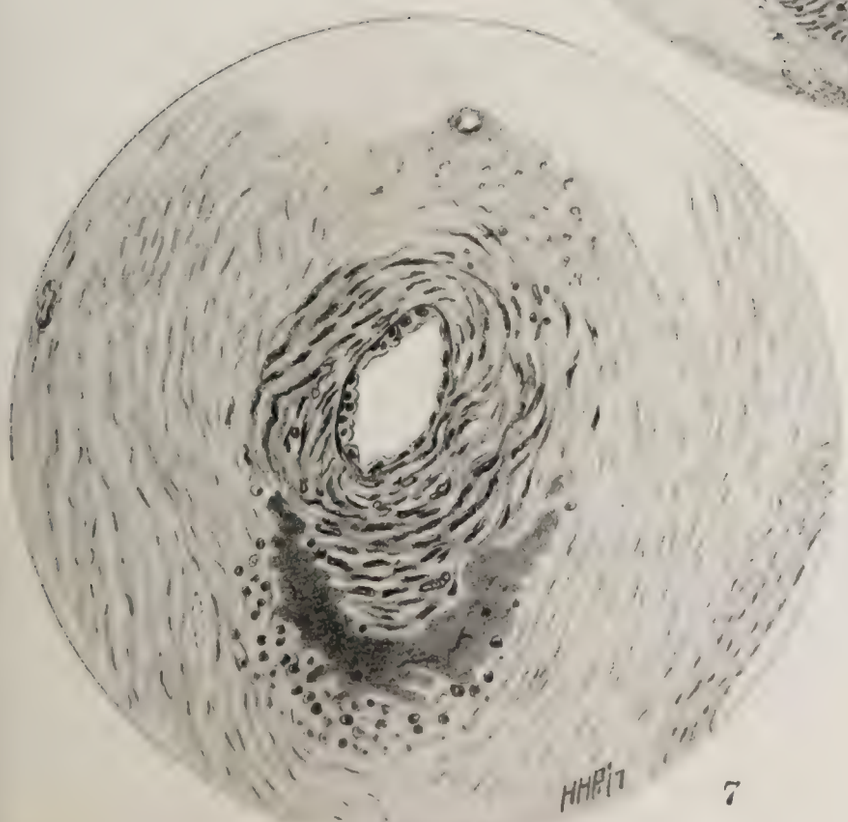

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Obsolete Miliary Tubercles of the Spleen

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OBSOLETE MILIARY TUBERCLES OF THE SPLEEN.

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Tuberculosis of the spleen is most commonly observed in cases of widespread miliary tuberculosis. In the not uncommon miliary disease of children and early adolescence, the spleen is usually involved in an intense infection of its tissues. Under these conditions the localization of the infection is mainly through a filtration of the blood by the spleen. The spleen, however, becomes only one of the many tissues in which the microörganisms locate. The tubercles which arise through the activity of this infection are all of about the same age, showing fairly uniform characters and common stages of development. At autopsy these lesions are seen in the acute or subacute stages, and are scattered in innumerable quantities through the spleen pulp.

The spleen also has been found to be the seat of primary tuberculosis. In the use of the term "primary" it is not meant that the spleen is the portal entry or even the first lesion induced by the invasion of the tubercle bacillus. The term is rather meant to suggest that the pathological process brought about in the spleen is more marked than found elsewhere, and not uncommonly the advanced tuberculous lesion of the spleen leads to a further dissemination into other parts. Thus not a few cases of the so-called primary tuberculosis of spleen show evidence of an older lesion in the thorax with, it may be, very recent tubercles in other tissues. The splenic lesion thus lies intermediate in time and has antedated some of the tuberculous processes of other organs. Not a few of the cases of primary tuberculosis of the spleen have been observed clinically and have received surgical intervention by splenectomy. In these cases it is obvious that although the splenic manifestations have been most prominent during life, no definite information can be offered as to the sequence of events in the tuberculous process. It is interesting that in these cases of primary tuberculosis of the spleen the organ is often found definately enlarged.

Autopsy No.	Sex.	Age.	Tuberculosis in organs.	Weight of spleen.	Fibrosis in spleen.	Nodules in spleen.	Previous history.
6	M.	42	Obsolete peribronchial glands and spleen	900	Fibrosis	One small calcareous	History of tuberculosis in family. Died of cirrhosis of liver.
6	M.	26	Obsolete spleen and liver	664	Adhesions	Numerous small hard and yellow nodules	No history of tuberculosis. Died of lobar pneumonia.
38	M.	42	Obsolete spleen.	95	Fibrosis.	Many small hard nodules, and one 0.75 cm.	No history of tuberculosis. Died of heart, kidney and arterial diseases.
40	M.	42	Obsolete peribronchial glands and spleen	260	None	Occasional small calcareous nodules	No history of tuberculosis. Died of pyemia.
51	M.	37	Obsolete tracheal glands, spleen and liver	240	Adhesions	Occasional small calcareous nodules and one in accessory spleen	History of tuberculosis not given. Died of chronic empyemia.
98	M.	61	Obsolete peribronchial, mesenteric glands, spleen and liver. Obsolescent of lungs and peribronchial glands	165	Fibrosis	Several small hard yellow nodules	No history of tuberculosis. Died of pernicious anemia.
103	M.	64	Obsolete spleen	160	Fibrosis	One small hard yellow nodule	Died of heart, kidney and arterial diseases.
105	M.	63	Obsolete lung, peribronchial glands, spleen and liver	75	None	Many small hard nodules	No history of tuberculosis. Died of apoplexy (arteriosclerosis.
107	M.	23	Obsolete lung, peribronchial glands, spleen and liver	70	None	Several small hard nodules	Died after severe accident.
122	M.	53	Obsolete peribronchial glands and spleen	140	None	Two small hard nodules	No history of tuberculosis. Died of gonorrheal polyarthritis.
134	M.	43	Obsolete lungs, peribronchial glands & spleen. Obsolescent lungs & retroperitoneal glands	215	None	Many small calcified nodules	Pneumonia two years previously. Died of acute lobar pneumonia.
146	M.	42	Obsolete liver, spleen and mesenteric glands	350	None	Two small calcified nodules	Died of cancer of duodenum.
152	M.	36	Obsolescent lung; obsolete liver and spleen	750	Adhesions	Many hard calcareous nodules	Died following railroad accident.
169	M.	48	Caseous tuberculosis of lungs with cavitation. Obsolete spleen and liver	90	None	One hard shot-like nodule	Died of chronic pulmonary tuberculosis.
173	M.	69	Obsolete lungs, peribronchial glands, liver and spleen	95	None	Occasional small calcareous nodules	Died of fracture of skull.
180	M.	43	Obsolete spleen	150	Adhesions	Two small hard yellow nodules	No history of tuberculosis. Died of acute toxic jaundice.
201	M.	26	Obsolete spleen	?	Adhesions	Many small calcified nodules	Died of diphtheria.
223	M.	20	Obsolete liver and spleen	130	None	Many small seed-like bodies	Died of acute nephritis.
242	M.	21	Obsolete spleen	225	None	Two firm nodules with pin-point areas of necrotic tissue in center	No history of tuberculosis. Died of bronchiectasis and abscess of lung.
298	M.	49	Obsolete spleen	85	None	Single firm yellow nodule	No history of tuberculosis. Died of acute lobar pneumonia.
300	M.	28	Obsolete spleen	190	None	Single hard nodule with necrotic center	No history of tuberculosis. Died of acute lobar pneumonia.
308	F.	39	Obsolete peribronchial glands and spleen	195	None	Many small hard nodules	No history of tuberculosis. Died of operative hematoma.
315	F.	70	Obsolete lung and spleen	75	Fibrosis	Some small shot-like nodules	History of chronic bronchitis. Died of bronchopneumonia.
333	F.	50	Obsolete spleen	140	Adhesions	Several small calcareous nodules	Died of acute lobar pneumonia.
349	M.	52	Obsolete spleen	200	Fibrosis	One small firm nodule	No history of tuberculosis. Died of syphilitic cirrhosis of liver.

Autopsy No.	Sex.	Age.	Tuberculosis in organs.	Weight of spleen.	Fibrosis in spleen.	Nodules in spleen	Previous history.
350	M.	30	Tuberculous bronchopneumonia. Obsolete and obsolescent peribronchial glands. Acute miliary lungs, spleen and liver. Obsolete spleen	300	None	Many small hard yellow nodules and many gray miliary tubercles	No previous history of tuberculosis. Died of acute miliary tuberculosis. Illness ten days simulating typhoid.
353	M.	25	Obsolete spleen	175	Adhesions	Many firm nodules with calcification	Died of Hodgkin's disease.
359	F.	18	Obsolete peribronchial glands spleen and lung. Obsolescent peri bronchial glands	130	None	Several hard fibroid nodules, size of mustard seeds	No history of tuberculosis. Died of acute gastro-enterocolitis.
360	F.	54	Obsolete peribronchial glands and spleen	115	None	One fibrosed nodule	No history of tuberculosis. Died of chronic cholecystitis.
413	M.	36	Caseous tuberculosis of lung with cavitation. Obsolescent peribronchial glands and intestine. Obsolete liver and spleen	225	None	Several hard calcified nodules, the size of mustard seeds	Died of chronic tuberculosis and pyopneumothorax.
422	M.	28	Obsolescent peribronchial glands and lung. Obsolete lung and spleen	90	None	Several small hard nodules, size of mustard seeds	Died of acute lobar pneumonia.
478	F.	36	Obsolescent peribronchial glands Obsolete liver and spleen	195	Adhesions	Numerous round yellow white nodules	Died of rupture of uterus.
480	M.	35	Acute tuberculous peritonitis. Obsolescent peri bronchial, retroperitoneal and omental glands, prostate and lung. Obsolete lung,spleen,liver and adrenal	?	None	Several hard round nodules	Died of tuberculous peritonitis.
516	M.	40	Obsolescent lung. Obsolete spleen and liver	250	None	Several small yellowish nodules	Died of acute lobar pneumonia.
522	M.	63	Obsolete peribronchial and mediastinal glands, and spleen. Acute miliary lung, kidney & spleen. Tuberculous ulcer of larynx	85	None	One small hard calcified nodule	Died of miliary tuberculosis.
534	M.	49	Obsolete spleen	125	None	Many fibrous and calcified nodules size of mustard seeds	Died of acute alcoholism and pneumonia.
541	F.	47	Caseous tuberculosis of lung with cavitation. Obsolete lung, peribronchial and mesenteric glands & spleen	125	None	A single firm white nodule	History of tuberculosis in family. Died of chronic tuberculosis.
567	M.	45	Obsolete spleen	360	None	Few small hard nodules	No history of tuberculosis. Died of appendicitis and peritonitis.
582	F.	42	Obsolescent peribronchial glands and adrenals. Obsolete peribronchial glands liver and spleen	?	None	Several small hard yellow nodules	Died of Addison's disease.
P–2898	F.	55	Obsolete spleen	175	Fibrosis	Several hard yelyellow nodules	History of cholelithiasis, jaundice, operation; death from hemorrhage.

To this group of tuberculous infections of the spleen must be added the one here under discussion, the healed or partially healed miliary lesion. Little or no note has been made by students on tuberculosis upon the healing of multiple miliary nodules within the spleen. The early stages of the development of the miliary tubercle is well known and has been much studied. These stages have been accurately followed through the proliferative reactions and the process of caseation. The growth of fibroblasts in the periphery of the advanced nodules has also been discussed, but few have reported observations upon the subsequent fate of the tubercle.

In our earliest observations upon the shot-like, mustard-seed nodules in the spleen we were unconvinced of their tuberculous nature. The fully headed nodule with its concentric layers of fibrous tissue and sharp demarcation from the surrounding spleen pulp, suggested a thrombotic origin of the fibrosis not unlike the formation of phleboliths in the pampiniform plexus of the testis. A further study, however, has given us an opportunity of seeing these nodules in the various stages of fibrosis. The lesions can be followed from the late caseous miliary tubercle with its surrounding fibroblasts to the definite encircling of the area with firm strands of connective tissue. Furthermore in some of the foci with advancing fibrosis evidence of the tuberculous process could be observed on the periphery in immediate contact with the sclerosing ring.

To the naked eye the obsolete lesion is characteristic. The shot-like yellow nodules stand in strong contrast to the spleen pulp. The sharp demarcation without an infiltrating fibrosis differentiates the lesion from other sclerosing processes. However, it is impossible by the naked eye to state whether such discrete nodules are fully healed or are only in the obsolescent stage. We have found that nodules, hard and shotty, may still contain within them small remains of caseous material or even evidence on the outer border of a reaction suggesting a still active process. It is, of course, possible that the nodules with peripheral reaction have become the site of a new infection.

The material forming the basis of this report was obtained from 404 autopsies on individuals over ten years of age. In this series of autopsies particular attention was given to noting the presence of tuberculous foci in all parts of the body. Out of the entire series, tuberculosis was noted in 172 cases. The spleen was involved in a tuberculosis process in 69 cases. Of these there were 40 instances in which healed or almost completely healed tuberculous lesions, subsequently to be described, were found.

Of the 40 cases there were 31 males and 9 females. The average age was forty-two, the youngest being eighteen and the oldest seventy. In all but 12 cases old tuberculous lesions were found elsewhere, most frequently in the peribronchial lymph glands or in the lung. In the majority of instances the individual did not suffer

from active tuberculosis and clinically no evidence of such infection was observed. Three patients, however, showed a persistent or chronic tuberculosis of the lungs; another died of tuberculous peritonitis, while 2 others died of an acute miliary tuberculosis. Other than these 6 cases the tuberculous lesion or lesions which were present elsewhere than the spleen were in the obsolete or obsolescent stage. In 28 cases an old tuberculous lesion outside of the spleen was found, and in the 6 cases suffering from active tuberculosis this antedated the recent dissemination. An interesting finding was the presence of healed miliary tubercles in the liver. Of these there were 15 cases, in 2 of which the liver and spleen were the only organs involved. These healed tubercles of the liver closely resembled those found in the spleen. They were small, round, and shot-like, without evidences of active tuberculosis in the organ.

Other than the characteristic tuberculous nodules in the spleen, this organ varied very much in its appearance. In weight it ranged from 76 to 900 grams. The average weight was 219 grams while there were twenty-four below 200 grams. As the finding of the old tuberculous lesions in the spleen was in the majority of cases only incident and as the individuals had died of various infections and accidents, the characters found within the spleen cannot entirely be referable to the old tuberculous lesions. It would appear from our table that the presence of this tuberculous process has no marked influence upon the weight of the organ. The presence of fibrous adhesions about the spleen or of an increase of the fibrous tissue within the spleen, was noted in 15 cases. Such fibrosis or adhesions may have been associated with the acute stage of the tuberculous infection; however, all of these changes cannot be referred to the tuberculous process alone, as cirrhosis of the liver and chronic infections probably played a part in changing the structural character of this tissue. There were many instances in which no characteristic change was to be noted in the splenic structure other than the isolated fibrous nodules of old tuberculosis. In 2 cases the old and discrete tuberculous processes of the spleen were associated with more recent miliary tubercles in the active and progressive stages. This would indicate a second dissemination of tubercle bacilli reaching the spleen.

The miliary tubercle of the spleen in the healed or almost healed state differs quite markedly in its appearance from similar lesions in other organs save the liver. It appeared in the character of a small nodule of hard consistence and usually spherical. The type most commonly met with appeared like a small yellow concretion about the size, shape, and color of a mustard seed. Occasionally larger nodules were found, of somewhat irregular shape and measuring up to about 0.75 cm. in diameter. These nodules were irregularly scattered through the spleen substance, and their yellow

color was in sharp contrast to the dark red pulp of the organ. They were found directly beneath the capsule or sprinkled through the parenchyma of the spleen. Their outer border was sharply demarcated from the spleen tissue, and they are quite easily removed from the surrounding structure. In their periphery there was no evidence of fibrosis extending into the surrounding parts. At times in shelling out the nodules the outer capsule was found to remain in the spleen tissue forming a small cup-like cavity. The discrete character of the nodules and the absence of change in their immediate vicinity was always striking.

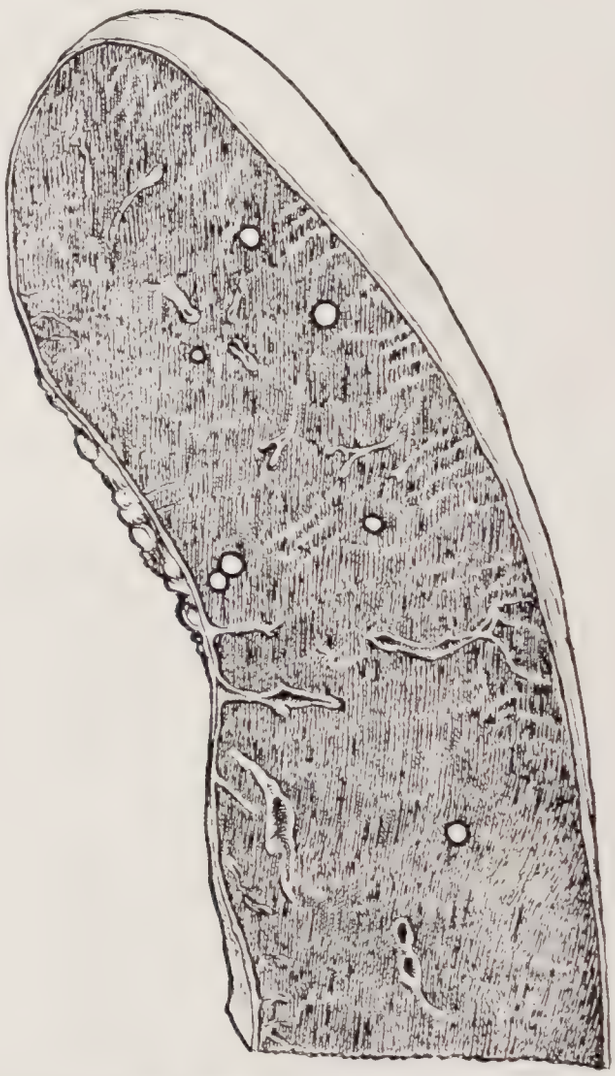

FIG. 1.—Spleen with obsolete miliary nodules of tuberculosis.

The number of these nodules varied from a few to a large number. Occasionally small clusters were found, but in the majority of instances the discrete masses were irregularly scattered at some distance from each other. The macroscopic appearance of the tissues forming the nodules have been fairly uniform. They were hard and shot-like, and the outer coats consisted of concentric layers of fibrous tissue which could be removed in successive laminæ. The centers of the nodules were either hard and calcareous or fibrosed, some of them still showing soft necrotic material. The necrotic substance when present formed very small, almost pin-point

areas in the immediate center. In a few instances a relationship between the nodules and the vascular channels was observed.

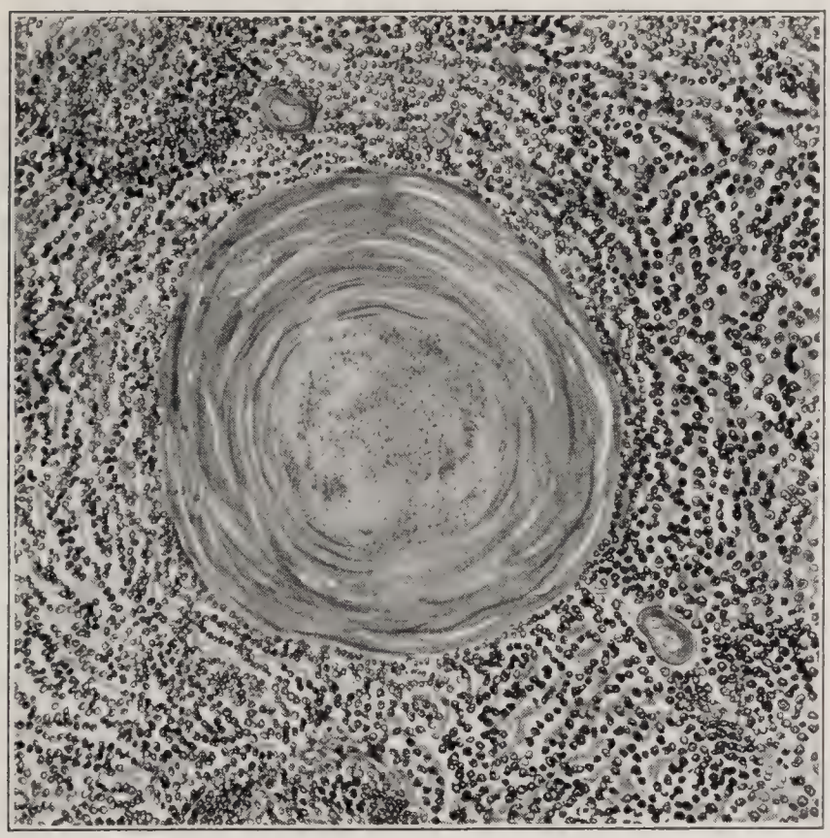

FIG. 2.—Fibrosed nodule with remnants of central necrosis.

FIG. 3.—Fibrosed nodule with central calcification.

The finding of 12 cases in which tuberculous foci were alone found in the spleen is remarkable. At first sight one would be tempted to suggest that the finding was dependent upon a careless search for other lesions. In a number of cases, however, a distinct

note was made at the time of autopsy that this was the only focus discovered. In these cases the splenic lesions differed in no way from those found in the remaining series.

There is one common characteristic possessed by all of the nodules which we have examined. This consists of the mature concentric layers of connective tissue which surround them and sharply demarcate the nodule from the spleen pulp. The spleen tissue immediately beyond the outer border of the nodule commonly showed no evidence of reaction, nor was its architecture changed. The fibrous tissue in the nodule did not send any trabeculæ into the surrounding tissue. This sharp line of demarcation in the absence of any response in the spleen pulp was quite remarkable. In some of the more recent lesions, those that had not advanced to complete healing showed more or less lymphocytic infiltration in the tissues immediaately surrounding the nodules, and in 4 instances this was accompanied by the presence of small and recent tubercles in the progressive and active stages. In some cases it appeared that these tubercles were associated with and dependent for their existence upon the main tubercles which had not reached the final stage of healing. In 2 instances recent tubercles were found in the spleen quite unassociated with the old nodules, but indicating a new hematogenous miliary distribution, as was indicated in the generalized miliary tuberculosis found elsewhere.

The size of the obsolete tuberculous lesions of the spleen indicated that during the active stage they consisted not of a single tubercle but of several closely approximated lesions. It is probable that, like the development of the ordinary miliary tubercle, the process began in a single tubercle, but with the development of necrosis and the multiplication of the tubercle bacilli a number of new tubercles were developed in the periphery. Thus numerous tubercles developed upon the circumference of the enlarging area until a size was attained which was readily distinguished by the naked eye.

The disposition of these old foci in the spleen was irregular and at times difficult to define. In some of them the remains of the central artery of the Malpighian body could still be seen within the fibrosed tubercle. These arteries were still patent and the fibrous tissue immediately bounding them was disposed in a direction concentric with the vessel. At other times it appeared as if the tubercle had developed within the pulp substance at a distance from the Malpighian body and unassociated with the trabeculæ of the spleen.

Although the nodules have, on naked-eye examination, a very similar appearance, and though they all have the common characteristic of being surrounded by a dense laminated connective tissue the central area may differ quite widely. In some the concentric layers of connective tissue continued throughout the nodule; others contained a small mass of granular necrotic material; the remains of former caseation in the center. The latter showed no evidence of an active process insofar as a tissue reaction was con-

cerned. The necrotic material was firmly bounded by a wide border of dense connective tissue without evidence of lymphocytes, endothelial cells, or giant cells. A varying amount of calcification was also seen in these areas of necrosis. At times this consisted of a fine granular precipitate while in others a definite concretion formed a central nucleus.

The manner of laying down of the connective tissue is interesting. In the early development of the miliary tubercle in the spleen the proliferative response giving rise to the new cells of the tubercle leads to the crowding aside of the essential tissues of the area. The fine reticular stroma with its lymphocytes and endothelial cells is pushed outward, so that in the immediate periphery of the tubercle they appear to lie in a concentric fashion. At this early stage there is no increase in this reticular tissue. Soon, however, this neighboring stroma without actual proliferation increases the thickness of its strands by the accumulation of hyalin or collagen. It has thus been not uncommon to find a peripheral border of a heavy collagen containing connective tissue forming a lacework surrounding the tubercle, from which the lymphocytes gradually disappeared. When the lymphocytes accumulate it is usually to the outer side of this stroma. This connective-tissue boundary continues to exist with the increasing growth of the tubercle, but not until a reparative process appears about the active foci does the original connective-tissue capsule increase to any definite degree. The laying down of new connective-tissue bands takes place on the inner side of this connective-tissue layer. Fibroblasts make their appearance in the small tubercles bounding the caseous center and gradually the characteristic architecture of the tubercle becomes disturbed until the giant cell lying within the jumble of fibroblasts and a few endothelial cells is all that remains of the active granuloma As the fibroblasts gradually lay down the permanent collagen fibers they are disposed in a concentric fashion. The disappearance of the fibroblast itself is rapid until nothing remains save the dense laminated collagen fibers. It was very apparent in these nodules that after the disappearance of the active process the new growth of connective tissue advanced but slowly. The caseous material in the center gave no evidence of tissue stimulation, and its absorption and removal was a slow procedure. Thus advancing fibrosis toward the center was a matter of time during which the central débris was being slowly removed.

Many sections of the fibroid masses, as well as of nodules with small caseous centers, were searched for tubercle bacilli but none were found. I would place no individual stress upon the negative finding obtained in material which had been stored in preservatives for more than a year, but as we have had similar results in dealing with tissues of more recent origin, I am inclined to view these strucures as devoid of infection. At what stage in the healing process the microörganismas are destroyed cannot be stated, but it is prob-

able that the event bears comparison with similar lesions in the lymph glands, as has been described by Warthin.

In 2 cases of recurrent infection of the spleen we have demonstrated tubercle bacilli in the progressive tissue lesions lying outside of the hard nodules, while no bacteria were found in the healed lesion. As we have previously stated these peripheral tubercles may have been a hematogenous reinfection of the spleen, or it may be that the bacteria had escaped from the primary miliary foci during the earlier stages of their development. In the latter case, if true, the infection remained latent over a considerable period, so that the difference in the tissue reaction between the primary and secondary lesion was very apparent.

Discussion. The evidence that we have here presented of healed or healing miliary tuberculosis of the spleen has an interest both from the clinical and pathological view-point.

In the majority of the cases the distribution of the tubercle bacillus to the spleen had taken place from small foci having no clinical significance. The findings indicate that the peribronchial glands were most frequently the areas from which microörganisms were disseminated by way of the blood stream. It is probable that, at the time of the bacillary distribution, several organs became the point of localization, and we have evidence that in 15 cases the liver was simultaneously involved with the spleen. In the majority of instances, however, miliary lesions of contemporary infection were lacking elsewhere. It is obvious that scattered miliary lesions induced in many tissues escape our eye after the process of healing is complete and when the local damage is of small extent. We cannot claim that in our series of autopsies all cases of healed miliary lesions of the spleen were observed, as isolated nodules may readily escape detection. It is, however, striking that as many as 40 cases should have come to our notice in a series of 404 autopsies on individuals over ten.

The absence of clinical data of any symptoms, whereby the time of infection of the splenic tissues can be indicated, gives us no opportunity of determining the age and rapidity of the healing process of localized miliary tuberculosis of the spleen. The early fibrosis developing about tuberculous areas after a period of six weeks or several months has been well studied in man and animals. Such reactionary fibroses, however, are still in the proliferative stage when fibroblasts and young connective-tissue cells are laying down an outer wall about the area of necrosis. The majority of lesions in our cases, however, were much more advanced and were devoid of evidence of active proliferation except in the instances where more recent recurrent infection had localized in the vicinity of the old lesion. The concentric bands of connective tissue were in the mature state, and in some instances in a process of hyaline transformation. Months of time would bring little alteration in their structure. It is well seen that such encapsulation would permit only of slow

organization of remnants of the caseous process. In some instances calcification of the central area supervened but in others a fine and granular necrotic material still remained. Whether any infection was still present in the central areas of necrosis could not be finally determined. We were unable to demonstrate tubercle bacilli in this material, but whether latent infection was still available must remain unanswered until inoculation experiments are undertaken. As the material with which we were dealing had been preserved from autopsies performed at different times in the past five years, we were unable to carry out all of the studies necessary to clear up many of these points.

A point worthy of comment is that the presence of these old tuberculous foci had no marked effect upon the uninvolved portion of the spleen. In a number of cases adhesions were found; in a few others there was fibrosis. By no means, however, was the fibrosis marked and often when noted it was more relative than real. Furthermore, in some cases the fibrosis had a direct relation to an intercurrent disease process. Likewise there was no constant evidence of splenic enlargement resulting from the presence of old tuberculosis. It has been indicated that in the so-called primary tuberculosis of the spleen one of the not unusual manifestations is the increase in weight and volume of the organ. The reported cases of primary tuberculosis of the spleen were observed in the acute or obsolescent stage. In these instances the focus of infection was of fair size, often occupying a considerable portion of the organ. Under these conditions the spleen showed definite enlargement. It is not uncommon that in acute miliary tuberculosis in which the spleen among other organs becomes the site of innumerable tubercles, its weight is materially increased. It may well be that during the acute process of infection of the cases reported in our series, the spleen was more or less enlarged. The condition, however, was transient leaving no characteristic organic change in its internal structure.

The distribution of the tuberculous infection was hematogenous. Whether the primary portal of entry was through the respiratory or alimentary system is immaterial. Undoubtedly, however, the infection primarily found localization in some other tissues where, after multiplication of the microörganisms and destructive changes in the involved structure, the bacteria found entrance into the blood stream. That no fatal outcome resulted at the time of this blood-stream dissemination indicated that relatively few bacteria were discharged from the initial focus. We have interesting evidence, therefore, that the quantity of infection of miliary tuberculosis varies greatly, and that the outcome of such distribution depends upon the relation between the amount of infection and the resistance of the tissues in which the bacteria locate. In these cases of old tuberculous foci in the spleen we have observed encapsulated nodules varying in number from one to very many.

A considerable interest has recently been taken in the role of the lymphocyte in tuberculosis. Bartel believed that he was able to demonstrate, by experiment, that a direct antagonism existed between lymphatic tissues and the tubercle bacillus. Primarily, it was found that a hyperplasia of the lymphoid structures along with an endothelial proliferation took place. These lymphatic tissues not only act as filters for the microörganism, but also offer a protective mechanism for the body. In many instances the infection of animal tissues by the tubercle bacillus is unassociated with structural change, even though the microörganisms are present in the tissues. Bartel has been able to demonstrate the tubercle bacillus within lymph glands in which no other change than hyperplasia had occurred. These bacteria he found were much reduced in virulence. Lewis and Margot found that there was a relation between the function of the spleen and the resistance of an animal to tuberculosis. Commonly after the inoculation with tubercle bacilli the spleen became enlarged. In mice it was found that splenectomy prolonged the life of the inoculated animals. No explanation could be offered for these apparently divergent results.

Ths importance of the spleen in counteracting infection, not only within its own tissue but also of a systemic kind, was shown in the experiments of Hektoen and of Simonds and Jones. These authors brought about partial destruction of the spleen by the application of the roentgen ray. After intense or prolonged exposure the animals developed a greater susceptibility for infection. This susceptibility appeared to be the result of a decrease in the lysins of the blood as well as a decided inhibition in the production and activity of the leukocytes. However, as the use of the roentgen-ray on small animals is not limited in its influence upon the spleen alone, it is possible that the change in the quantity of immune bodies is also dependent upon the effect of the rays upon the other hemopoietic organs. Somewhat more confusing results have been obtained by the use of benzol. This substance has a marked influence in depressing the production of leukocytes by the bone marrow, at the same time it was shown by White that prolonged treatment of rabbits by benzol led to the development of a much enlarged spleen. This occurred even when the leukocytes of the blood had been reduced more than one-half. Under these conditions of an enlarged spleen and diminished leukocytes the animal showed an increased susceptibility to the tubercle bacillus as compared to the untreated animals.

There appears, therefore, to be good evidence that the spleen has a definite relation to the development of immune bodies in various animals. This function is probably a limited one, and is similar to that possessed by other hemopoietic tissues. Whether the resistance of the spleen to infection differs greatly with the various microörganisms is not clear, but it would seem that, like other lymphatic tissues, its antagonism to the tubercle bacillus is quite marked.

Of the 40 cases of healed miliary tubercles of the spleen, 15 showed similar lesions in the liver. The liver nodules were identical with those in the spleen, being round and hard and of the size of mustard seeds. They were distributed irregularly through the liver substance, and usually were few in number. More frequently they were found in the periphery of the lobule, in direct contact with the fibrous tissue of the portal systems. Their sharp demarcation from the surrounding liver tissue was as striking as in the spleen, and the absence of associated tissue change in other parts of the liver was constant. Whether the microörganisms located in the liver at the time of the general hematogenous distribution, or whether the liver infection was gained by the portal blood from the spleen cannot be stated. Both routes of infection are available, and a portal distribution during the active process in the spleen might readily occur.

In view of the high incidence of liver infection in all cases of tuberculosis, as is claimed by some, it is remarkable that healed miliary nodules do not appear more frequently. If, as Ullom states, tuberculosis of the liver develops in from 70 to 100 per cent. of the cases, the mode of distribution must in large part be hematogenous, and Rolleston believed mainly by the portal vein. In our own observations we have failed to find tuberculosis of the liver as frequently as stated, though we have never undertaken a systematic search by the microscope. As is observed by all, the tuberculous lesions of the liver are most often of insignificant size and discovered only by microscopic search. The lesions which we have observed associated with the spleen nodules were all recognized by the naked eye at the autopsy table. Their character was so uniformly similar to those in the spleen as to suggest a synchronous deposition. Moreover, they would also indicate a tissue resistance to this infection equal to that of the spleen, suggesting a systemic as well as a local organic origin for the immunity. In no instance where healed miliary tubercles were found in the spleen had the liver infection progressed to conglomerate tubercles or cavitation. Even in those cases of pulmonary tuberculosis in which the tissue progressed to caseation and cavitation of the lungs the foci in the liver and spleen remained small and were well advanced in healing. These differences in the healing process of various tissues offer interesting studies in tissue immunity.

We find but little reference in the literature to the presence of healed miliary lesions in the spleen. Abbott in the *Catalogue of the McGill Medical Museum* mentions one specimen presented by Adami of the character as we have described. In an analysis of 1000 autopsies Adami and McCrae found evidence of healed tuberculosis in 151 cases and of these, healed lesions were present in the spleen twice while obsolescent lesions were seen four times. Winternitz has given a very full review of the work on tuberculosis of the spleen, in which he makes particular reference to the so-called primary tuberculosis, a condition quite different from that which

we have under discussion. The lesions described by him usually refer to large caseous masses which have led to much enlargement of the spleen to be recognized clinically. A considerable number of these cases were treated surgically by splenectomy. Although the spleen is spoken of as the seat of acute or subacute miliary infection no reference is made to the healed lesion. The frequency of splenic involvement in tuberculosis is given by Reinhold, who found tuberculosis of the spleen in 67 per cent. out of 428 cases of tuberculosis in children, and in 19 per cent. out of 836 cases in adults. In our own series of 404 autopsies tuberculosis was present 172 times and the spleen was involved in 69 cases. In 40 of the latter healed miliary lesions were found in the spleen, 2 of them showing a reinfection with a fresh crop of tubercles. Sternberg in a discussion upon peculiar types of tuberculosis with characters of pseudoleukemia noted the tendency to fibrous encapsulation of tuberculous processes in the spleen. Colet and Gallavardin referred to the finding of partly sclerosed nodules in the spleen of a man, aged sixty years. The liver in this case also had nodules which were still caseous. The report on focal tubercuolsis of the spleen by Fischer deals with subacute lesions in which caseation occupies the center of the nodule while the periphery is made up of proliferating epithelioid and giant cells. None of the lesions observed by him had reached the obsolete stage. Brohl excised the spleen of a patient aged forty-eight years, and found six small yellow concretions which contained calcium carbonate and phosphate, and which he believed had their origin in phleboliths.

More comparable to the described lesions of the spleen are those reported by Warthin occurring in the mesenteric glands. Warthin claimed to find evidence of healed tuberculosis in the mesenteric glands with great frequency. The tissue changes consisted in part of hyaline deposits as well as small fibrosed nodules with central débris and a peripheral laminated structure. The latter lesions appeared very similar to those which we have observed in the spleen. On no occasion, however, have we found the centers to consist of a hyaline substanec. The hyaline transformation of the neighboring stroma was frequently observed in the spleen in the presence of tuberculous foci. Warthin found similar hyaline and sclerosed masses in the bronchial glands of adults.

A word must be said about the 12 cases of healed miliary tuberculosis of the spleen in which no other focus was found in the body. As we have previously indicated, search was made at the time of autopsy for other tuberculous manifestations, and none were found. We cannot but doubt that some unrecognized focus had existed near the point of entrance of the infection, but that recognizable tissue change was no longer evident. The splenic infection had undoubtedly developed through blood infection in which other organs had also received localized foci. It would appear that the tuberculous process had been dealt with unequally in the various tissues, all

save the spleen clearing themselves of the invading organism before permanent damage was done. In the spleen, temporary tissue destruction was brought about with subsequent complete healing. In these cases it would appear that the resistance of the spleen to tuberculous involvement was not so great as in other tissues. These findings would indicate that a tuberculous bacteriemia may occur in the absence of an advanced localized focus of infection and that a miliary distribution may be overcome by the individual tissue resistance.

Conclusions. In a series of 404 autopsies, tuberculosis was met with in 172 cases. The spleen was involved 69 times, and in 40 of these miliary lesions were completely or almost completely healed by fibrosis.

The average age was forty-two years and the youngest was eighteen years. Six of the cases showed a persistent tuberculosis in other organs. In 15 cases the liver also contained healed miliary tubercles.

In none of the cases had there been recognizable clinical manifestations of splenic involvement. The spleen was not enlarged. In 12 cases with healed miliary tubercles of the spleen no other tuberculous process was found.

The splenic infection was a hematogenous one arising most commonly from antecedent foci in the lungs or peribronchial glands. Those cases in which no primary tuberculous focus was found probably had a similar mode of origin in which, however, the initial focus was of minor extent unrecognizable at the time of autopsy. We would point out that the fibroses which are observed in anthracotic peribronchial glands are difficult of analysis as indicating a preceding infectious origin of the fibrosis.

The healed splenic tubercles are recognized only by careful search and complete gross sectioning of the tissues of the organ. The presence of the healed miliary tubercles of the spleen indicates the frequency of a tuberculous bacteriemia from which the tissues may entirely recover. The different organs demonstrate a variable resistance to the tuberculous infection. Reinfection may take place in the spleen.

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ACUTE DEATH FROM CHLORINE POISONING

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ACUTE DEATH FROM CHLORINE POISONING*

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THE study of the effect of chlorine gas poisoning is one that has been introduced by the present war. Prior to 1915 there are but two or three references in literature concerning the harmful action of chlorine upon health. To have undertaken an extensive study of chlorine poisoning, would have been looked upon as an academic occupation of one who had difficulty in finding a problem of active interest to human welfare. Suddenly, however, the medical officers, serving on the battlefields, were confronted with the direful effects of chlorine and other gas poisonings for which their studies in therapy had given them no adequate remedy. In the absence of knowledge of the manner in which these irritating gases produce their effects, the resources of chemists and physicists were called upon, to offer a means of prevention. Our hopes along this line of endeavor have been greatly raised by the introduction of adequate masks. Nevertheless, before these became available, much harm has been done both through the gruesome method of killing men, as well as the permanent injury inflicted upon those receiving a lesser concentration of gas. Chlorine appears to have been used most extensively, but bromine, phosgene and other gases have also been used.

The horror of the first gas poisonings led to a number of investigations by British authors. These studies have been of an experimental kind and considerable information has been gained as to the manner in which chlorine attacks the tissues. Schaefer has exposed animals to chlorine gas varying in concentration from 1 to 20 per cent. Such concentrations are unusually high and it is improbable that any of the soldiers at the front have ever found themselves in an atmosphere containing this amount of chlorine. It is more likely that the human gassings are accomplished in a concentration of 1:1000 to 1:10,000. However, each gas raid by the Germans must vary in the actual amount and concentration of gas which reaches the allied forces. The efficiency of gassing by chlorine rests to a large extent upon the climatic conditions, there being necessary a favorable breeze sufficient to waft the liberated chlorine towards the opposing trenches, but with the air currents inefficient to stir up the heavy gas from its low lying position over the terrain to cause excessive diffusion. Furthermore, the concentration of the gas will be materially altered if on the morning of its use, the ground be damp and the air contain much fog. The great solubility of chlorine gas in water permits its rapid removal from the air.

Schaefer's important observations on chlorine poisoning may be summarized as follows. The immediate effect of chlorine gas is to irritate the mucous membranes with which it comes in contact and particularly the bronchioles. The bronchial tubes did not appear to alter the size of their lumina by muscular contraction and Schaefer did not believe that the dyspnea was referable to the contraction of the air tubes. It was observed that the main effect of the inhalation of gas was upon the lung structure wherein the capillaries responded in an

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unusual dilation followed by edema of the alveolar walls and the air sacs. With this pulmonary congestion, there was a marked drop in the systemic blood pressure, which, in the absence of a primary cardiac failure, indicated some resistance to the blood flow from right to left heart. Schaefer refers to this occurrence in the terms of an "obstruction in the pulmonary vessels rendering it impossible for the blood to pass freely to the left auricle and ventricle." He was unable to indicate the exact manner in which this pulmonary obstruction was brought about.

Shortly following this, Leonard Hill also studied the problem of gas poisoning, paying particular attention to the effects of chlorine. His viewpoint differs somewhat from that of Schaefer. Broadly, his attitude is that chlorine is a definite irritant, acting not unlike a burn. In other words, the application of chlorine to tissues will simulate in its reaction other irritants which induce various grades of inflammation. The exact quality of the reaction will be determined by the amount and concentration of the irritant substance. Thus, at times in high concentration, chlorine will destroy the cells with which it comes in contact. The bronchi and bronchioles may be denuded of their epithelium, and the irritation of the gas upon the deeper structure of the bronchioles will lead to muscular spasm unless the gas has destroyed these elements. Hill thoroughly agrees with Schaefer that, since chlorine is such an active chemical agent which can find so many substances with which it can unite in the blood, it will not be carried in the free state to distant parts. Thus it is hardly probable that chlorine, as such, damages distant tissues, but only accomplishes serious organic lesions, such as described by Broadbent in the kidney, through indirect means. Hill, furthermore, observed that at the beginning of the experiment, when chlorine was first given the animal, the expansion of the chest was diminished, which he believes was due to the contraction of the bronchial tubes. Congestion and edema of the lungs followed, appearing first in patches and then spreading. The blood became venous and the output through the lungs was lessened. If the edema of the lungs was forcibly removed by pressure, the condition of the animal was greatly improved.

The problem concerning the deleterious effects of chlorine bears a direct relation to respiration and the pulmonary circulation. For the present, we will not concern ourselves about the secondary manifestations which may arise in a vicious circle. It is clear that systemic poisoning does not occur, and the distant effects, whatever they be, are in large part the result of the intrathoracic pathology.

Hill describes a typical human case of gassing as one that is "cold with a subnormal temperature, conscious but restless, with pulse slow and full (except in the collapsed cases). The face is cyanosed, intensely so in many cases, and the expression strained and anxious. The posture varies. In some cases the patient sits propped up, with head thrown back, gasping for breath; in others, he lies on his side, with his head over the edge of the stretcher in an attempt to aid expectoration. The respirations are jerky and hurried, often numbering 40 a minute, and are associated with a choking cough, accompanied by a varying amount of frothy expectoration. With each inspiration the chest is expanded to its fullest, all the auxiliary muscles being brought into play just as in an asthmatical paroxysm. This is the first, or asphyxial, stage, which, if the pa-

tient survives, gradually passes off after some thirty-six hours. After the first stage the patient falls into a sleep, and awakes feeling much better. But after a few hours of comparative quiet, symptoms of bronchitis begin to manifest themselves. In the majority of cases these are not severe, because, no doubt, nearly all the severe cases die in the first stage. In the cases that are kept alive with difficulty there is a short quiescent stage followed by intense bronchitis. The frothing gives place to greenish mucopurulent expectoration, consciousness to delirium, the temperature rises from subnormal up to 104° F., the pulse becomes of small volume, with its rate increased perhaps to 160, the respirations are less choking but more shallow, and number up to 70 a minute before death."

This description of gas poisoning in man is very similar to that noted in animals. When guinea pigs are exposed to 1:1000 chlorine gas, evidence of irritation is seen in the watering of the eyes and in the attempts on the part of the animal to seek a position away from the fumes. For a time, the animal appears to be holding his breath. Soon, however, he is forced to inspire, causing him to cough and sneeze. With this, there is a watering of the nose, and the animal paws his face as if to brush away the irritant. The respirations now become more rapid but jerky; there appears to be some difficulty in breathing and the thorax is held quite rigid while the costal borders tend to flare and shallow respirations are carried on mainly by the diaphragm. The animal is distinctly distressed, and gives intermittent gasps. If at this stage the animal is removed from the chlorine mixture, the gasping continues for some time, even hours, as he is recovering. If the animal has been overexposed the gasping continues after he is in the free air, until death. When allowed to remain in the gas mixture, the respirations shortly before death become hurried and then suddenly cease. During this time the heart beats regularly and continues for some time after the cessation of respiration.

Acute chlorine gas poisoning may be induced in small animals, mice, guinea pigs, and rabbits in concentrations of from 1:10,000 to the stronger mixtures. For careful observations it is well not to use mixtures of a greater concentration than 1 per cent. The main differences that we have noted in the various strong concentrations of chlorine gas have been in the rapidity of the onset of the symptoms and the time of death. In the very acute cases, death occurs in 3 minutes; with the less concentrated mixture, rabbits, guinea pigs, and mice will survive for half an hour or longer.

Some observations were made upon the blood of gassed animals. As we have stated above, chlorine is not absorbed and distantly distributed in the free state by the blood. In a previous study by Miller, it was shown that a definite lymphocytosis was present in cases of chronic chlorine poisoning. These chronic cases were soldiers who had survived the gassing for several weeks or months. In the acute cases, as was observed in one of his cases no lymphocytosis was present. He believes that an increase in lymphocytes was due not to the direct effect of the chlorine gas but was the result of chronic inflammatory changes in the lungs. When chlorine gas, even in very low dilution, is permitted to come in contact with blood, its active reducing qualities are quickly noted. The blood in contact with the chlorine becomes black and gummy and on long exposure is decolorized. By passing small quantities of chlorine through a blood solution, the coloring matter is entirely destroyed and the iron is liberated in the watery

solution. Hake demonstrated this free iron by Prussian blue test. He suggested that this marked effect of chlorine on the blood, might have some relation to its lethal effect. In none of our animals have we been able to demonstrate such profound blood changes referable to the chemical effects of chlorine.

On the other hand, an interesting observation was made upon the cellular content of the blood of the treated animals. When mice were exposed to the lethal concentration of the chlorine gas, it was found that immediately after death, the congested areas of the lung contained but small quantities of fluid blood. The congested areas stood out prominently and did not shrink or collapse. The tissues were edematous and there was frothy fluid in the bronchial tubes but the blood within the congested portions of the lung substance appeared coagulated. On several occasions we were surprised to find that this coagulation proceeded into some of the larger vessels. The right heart, both auricle and ventricle, was dilated and continued beating after cessation of the respirations; the left heart was in firm systole. The systemic circulation had ceased and respiration was no longer maintained, owing to cerebral anemia. It appeared as Schaefer intimated, that there was some obstruction in the pulmonary circulation. It was difficult at first to account for such an obstruction when in truth the vascular channels in the lung were in a state of congestion. Here, however, there was evidence that in these cases of acute poisoning, the stage of congestion was only an early manifestation of the irritating effects of the gas and that this congestion was succeeded by a stage of intravascular coagulation. The pulmonary tissue responded to the irritant, with a type of inflammatory exudate in which large quantities of serum escape from the dilated capillaries and permeate the alveolar walls and air sacs. The acute deaths in animals were always accompanied by a remarkable pulmonary edema. The lungs were waterlogged and the alveoli filled with a thin frothy fluid.

Even with the intense congestion of the lung we have never observed hemorrhage sufficient to tinge the edematous fluid. The remarkable rapidity and extent with which this edema develops, suggested the possibility that the abstraction of water produced marked changes in the blood within the pulmonary capillaries. The possibility that this abstraction of water and consequent thickening of the blood increased the viscosity and led to the excessive resistance of the blood flow in the lungs is in agreement with the findings of Schaefer and the demonstration of the right heart embarrassment. It, furthermore, occurred to us that the abstraction of these relatively large quantities of fluid from an engorged system of vessels would not only increase the density of the plasma but would also bring about a change in the numerical cellular content of the blood. That this was the case was demonstrated in blood counts made from the pulmonary vein of the gassed animals (mice and guinea pigs), such counts showing an increase of from two to five million red cells over the normal count. It was found, therefore, that the obstruction in the pulmonary circulation referred to by Schaefer was in part at least due to the increased viscosity of the blood.

There is, however, another factor of much graver importance affecting the pulmonary circulation. As we stated above, the congested areas of the lungs were found to contain less fluid blood than would be expected from their appearance. From the character of the dry congested tissues of the lung it was evident that the blood had coagulated within the dilated capillaries. This state

we found only in the severely and fatally gassed animals. As we will mention later, microscopic evidence of such coagulation was obtained. This unusually rapid coagulation may be the result of the intense edema whereby the blood constituents within the vascular channels are greatly altered and concentrated, permitting of rapid spontaneous solidification. On the other hand, chlorine gas, when in contact with fluid blood, tends to coagulate it almost instantly. We have found that human blood placed in an atmosphere of 1:1000 of chlorine coagulates in about fifteen seconds; stronger concentrations reduce this time. It is probable that within the lung where, through congestion and edema a slowing of the capillary circulation has already taken place, and where because of the great abstraction of water from the local tissues, the blood is in the threshold state for coagulation, the local and direct effect of chlorine upon the capillaries and blood materially hastens coagulation.

In as much as in our experimental animals the respirations ceased before the stoppage of the right heart, and as Schaefer has shown that there is a distinct drop in the arterial blood pressure, it would appear that the acute deaths of the experimental animals were the direct result of obstruction of the pulmonary circulation and that the presence of the pulmonary edema was a factor in this regard.

But, however, all of the acute deaths taking place from a few minutes to an hour after exposure observed in human cases are not as intense as those described. Under those circumstances where the individual continues to live for an hour or two, the fatal result is more particularly associated with the edema and consequent asphyxia than to a direct embarrassment of pulmonary circulation, although undoubtedly the increased viscosity of the blood associated with pulmonary edema also plays a part.

Our microscopic analyses substantiate the above findings and indicate that the important changes take place in the lungs while tissues elsewhere in the body are not directly affected by the gas. We have repeatedly observed the absence of congestion in the abdominal organs, though in animals surviving some hours after gassing, the liver showed a mild grade of engorgement. This was in consequence of the inability of the right heart to carry on an adequate circulation through the lungs.

The reaction (microscopic) in the lung varied according to the length of time of exposure to chlorine and with the concentration of the gas used in the experiments. The mildest reaction consisted of congestion, effecting particularly the capillaries of the alveolar walls and also the larger blood vessels, both arteries and veins. When the congestion had continued for longer periods of time, an edema made its appearance within the air sacs. This edematous fluid is of a very watery nature and of low albuminous content. The alveoli are flooded with this fluid and when it persists, a gradual shrinking in the size of the alveoli takes place. Concurrently with the appearance of this edema, scattered portions of the lung become emphysematous. These emphysematous alveoli become widely stretched, and are devoid of fluid. In this stage, congestion, edema, and some emphysema are the outstanding pulmonary changes. It is to be remarked that although the congestion is very intense and has an appearance as if the small alveolar capillaries would rupture, it is but rare to

observe the presence of red blood cells within the air sacs. On the other hand an escape of red blood cells may take place into the alveolar wall itself.

A direct influence of the action of the gas upon the cells lining the bronchi and air sacs, was not frequently observed. In only a few instances, was there evidence of desquamation of a few cells of the bronchial epithelium or a change in the morphology or staining qualities of the alveolar lining cells. True coagulation necrosis was not observed and there was nothing to indicate that the contact of the gas on the mucous membranes was of particular importance in bringing about a serious pulmonary condition.

An important observation in the acute deaths, particularly in mice, was the finding of patches of diffuse coagulation of blood in the pulmonary capillaries. In these areas we have observed within the capillaries and larger vessels the presence of a diffuse meshwork like altered fibrin. Wide stretches of channels were found in which an irregular meshwork of threads stained diffusely blue with hematoxylin. In these thrombi relatively few red blood cells were found. Similar coagula with a varying number of erythrocytes were seen in the arterioles and venules. This process of thrombosis was not uniformly distributed through lung.

In those animals receiving smaller quantities of gas or in which the gas concentration was less, the fatal results were variously delayed, with this delay in time of death a considerable difference was noted in the pathologic histology of the lung. The congestion was found persisting but of a different grade of intensity although sometimes the congestion appeared equally marked as that seen in more acute experiments. The edema also persisted in different degrees, but more commonly there was a tendency for the disappearance of the watery fluid contained within the alveoli. It was not uncommon, however, that a new type of edema made its appearance. This occurred as a tissue edema, surrounding blood vessels, and to some extent around the bronchi. The perivascular lymph spaces were widely dilated, developing a loose structure around these tubes. This late edema was accompanied by a more or less inflammatory reaction in which lymphocytes and occasionally leucocytes and plasma cells were found in the fluid of the tissue spaces. Inflammatory reactions were not alone present in the perivascular tissue, but were also present in the alveolar walls. following the congested capillaries. Here again the lymphocyte was the most common cell. Leucocytes were not abundant. Endothelial cells were occasionally found within the alveoli. The extent to which the cellular exudate made its appearance in the pulmonary tissues appeared to vary, not only with the manner of exposure to chlorine, but also with the individual susceptibility of the animal. In some animals, the perivascular ring of edema became intensely packed with lymphocytes, so that a crown of cells surrounded the medium-sized vessels. At times this was seen around the bronchi and occasionally the intervening air sacs contained a similar exudate.

To sum up, the acute reaction found in the lungs of animals exposed to chlorine consisted mainly in an intense congestion with edema and capillary thrombosis. Animals surviving a longer period showed a pulmonary infiltration of inflammatory cells mainly lymphocytes. The acute capillary thrombosis appears of importance in the acute deaths when the concentration of the gas is great. The intense pulmonary edema obtained by abstracting a thin serum from

the pulmonary blood vessels causes an alteration in the quality of the blood and an increase in its viscosity. This dense blood tends to clot spontaneously and is also influenced in this more rapid clotting by the presence of chlorine within the lung. These two factors, increased viscosity and capillary thrombosis, impede the ready flow of blood through the lung and lead to a fall in the arterial blood pressure. Thus, acute chlorine gassing differs materially from other forms of asphyxia.

Further studies are in progress with particular attention to the subacute and chronic types of death. I am indebted to L. E. Ramsey for practical assistance in this work.

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Portal of Entry and Route of Infection in Tuberculosis in Children

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PORTAL OF ENTRY AND ROUTE OF INFECTION IN TUBERCULOSIS IN CHILDREN *

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The problem of the mode of infection has been before the medical world for many years, and has formed the topic for research for many investigators. The nature of the infecting agent in tuberculosis has been known to us since 1882, the presence of the tubercle bacillus in a variety of discharges constituting sources of infection is well appreciated, the distribution of the micro-organism through different media has been demonstrated, while the nature of the lesion induced in the human body has been thoroughly investigated and reported by a great many. These studies have given us a clear conception of particular phases of the problem of tuberculosis, and relatively little concerning the practical side of the question remains. True it is, points of interest in other fields will keep awake the inquisitive spirit which is unwilling to rest until tuberculosis in man has been conquered, controlled or eradicated. But with all the tremendous work on these phases of the problem, there is no cordial agreement on the question of the mode of infection. Formerly, it is true, the confusion was greater than re-

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mains at present. We have sifted the evidence from many sources so that today our problem resolves itself into the interpretation of a few points, towards which it is necessary to collect more data before a final conclusion can be drawn. Individual statistics are insufficient to give the answer to many of these intricate problems in the biological sciences, for many are warped by factors not under the control of the investigator or are colored by personal enthusiasm. This has been so true of the problems in tuberculosis, not only in the work of transient investigators, but also in the teachings of authorative exponents.

In considering the mode of infection by any micro-organism we are not justified in drawing our conclusions until all the variable constants or the factors which modify the means of this infection have been clearly considered. This is not only true in tuberculosis, but also with the great variety of micro-organisms pathogenic to man. The unequal distribution of disease in various localities, at various age periods or in different tissues of the body has its definite reason governed by exogenous or endogenous circumstances. In the problem of tuberculosis, some very dogmatic statements have been made regarding the appearance of the tuberculous process in certain tissues of children as compared with those of the adult, and although the facts as presented by different observers are correctly shown, yet the inferences are most various and often erroneous.

It is well to appreciate at the outset that man may become infected by the tubercle bacillus in

his tenderest years until the last days of ripe old age. To what degree there is a definite difference in susceptibility or tissue resistance is very hard to say. It is true that the frequency of active tuberculosis is not uniformly distributed through all periods of life, but this finding that the frequency of tuberculosis is higher at one time than another is insufficient proof of varying susceptibility. A very important factor and one which deserves the greatest attention is the opportunity which confronts each individual during his life for gaining infection. For some individuals, the children of tuberculous parents, the opportunity from the very day of birth for receiving tubercle bacilli is very great.

The examples of tuberculosis in the first few months of life are not so uncommon, and, in them, infections of the lung with or without generalized dissemination has been the reported type. But even if the child of tuberculous parents escapes infection during the first year, he is still imperiled during all the years that he remains in the care of a tuberculous household. But again we cannot draw too sharp a conclusion respecting the dangers of tuberculous infection from parent to child, as these dangers are in inverse ratio with the intelligence of these parents. The experiments of Bartel, showing that the rooms of tuberculous adults contain tubercle bacilli in sufficient quantity to give rise to tuberculosis in experimental animals when permitted to run about on freshly dusted carpets, are only evidence of the unsanitary house-

hold and deportment of the inhabitants. The mother with active tuberculosis, coughing over her infant in arms, can hardly hope for other than a tuberculous child. Naturally, these types of contact infection propagate the same form of tuberculosis, the human type, as is present in the original lesion. The statistics of Park and others indicate the frequency of such infection in the finding of twenty-three strains of the human bacillus in the lungs of children under 5, while there was only one similar infection due to the bovine type. Between the ages of 5 and 16, eleven human strains were obtained from the lungs, and no bovine type has as yet been isolated. As we shall point out later, we believe that these infections by the human tubercle bacillus were gained through the respiratory tract and that the alimentary tract in these pulmonary infections is a negligible quantity. I have had an opportunity of seeing only a few cases of active pulmonary tuberculosis in children under 2 years, but in these cases, the picture resembled that of the adult pulmonary type without evidence suggesting the alimentary route.

In his study of the manner of gaining infection by infants, La Fetra has found some interesting facts. The cases analyzed were, for the most part, in children under 12 months of age. Seventy-three cases of pulmonary tuberculosis which were so proved by analysis were shown to have been in children in the care of tuberculous parents, friends or nurses in 43.8 per cent. Similarly of fifty-eight children having tuber-

culous meningitis, thirty-six of whom also had definite lung lesions, 36.2 per cent. had been cared for by parents, friends or nurses with active tuberculosis. It is remarkable that this author was able to trace so many of the cases to their sources, and when we remember how frequently the exposure to a given infection may occur without our knowledge, it is with some surprise that a definite source was established in virtually 40 per cent. of all cases.

The child, however, enters an important period of its life after leaving its mother's arms. This is the time when the child, having been weaned, has a large part of its nourishment offered in the form of milk, raw or treated. The actual amount of milk which a child consumes during these years can readily be worked out for each, and when we then consider that at least 6 per cent. and more commonly from 10 to 12 per cent. of the milk received in cities contains bovine tubercle bacilli, there must be a very fair proportion of infected food received by the child. The actual number of tubercle bacilli ingested naturally varies. There may be periods when on a particular day the content of organisms is unusually high. We have at present no ready means of estimating the bacillary content, of the type under discussion, in our daily milk. Granted even that the milk is treated, there is always the danger of error in the technic or carelessness in the use of utensils. Undoubtedly, the protection afforded by pasteurization assists largely in minimizing the danger from infected milk, but it is only too

true that much of the milk forming the diet of young children is offered in a raw state.

It is easy to appreciate the difference in the incidence in various communities of childhood tuberculosis, due to the bovine tubercle bacillus, based on the varying amount of tuberculosis in cattle and tubercle bacilli in their milk. We can hardly compare the statistics of Germany, Japan and the United States in as far as the incidence of tuberculosis arising from infected milk, because of the very great difference in the frequency of tuberculosis in the cattle of these various countries. It is extremely rare to have spontaneous infection of cattle by the human tubercle bacillus and we may accept it as the rule that the tubercle bacillus of milk is of the bovine type.

Here then the child is confronted by a new source of danger which in its earlier days was wanting. Not only does the infant run the gauntlet of an infection by the human bacillus from parents and associates, but now in childhood has a certain added danger of infection from food. It is during this period that the highest incidence of primary abdominal tuberculosis is recorded. Statistics on the subject are misleading, and in considering the frequency of primary pulmonary and primary abdominal tuberculosis in childhood we must be careful to consider only those cases in which there is undoubted evidence of the portal of entry. We are agreed that there is no hindrance to the development of primary tuberculosis of the lungs; likewise that a primary lesion may

occur in association with infection by the alimentary canal. But a confusing factor arises in that from each of these primary sources secondary invasion may occur in distant foci including these sites themselves. It has been repeatedly shown that although children usually have but little sputum in pulmonary diseases, a secondary infection of bowel is not uncommon through the swallowing of the pulmonary discharges. To what extent the intestinal infection may give rise to pulmonary lesions is far from clear. In children under 5 the bovine bacillus has been isolated thirteen times from abdominal lesions, but never once have these given the presence of the bovine bacillus in the lung. On the other hand, the simultaneous presence of pulmonary tuberculosis and intestinal lesions due to the human bacillus are common.

It is pointed out by Woods Hutchinson that the belief, that while the pulmonary form of tuberculosis is both the commonest and the most frequent cause of death in adults, this is not the case in children, is erroneous. He also points out the error in the belief that certain organs and groups of tissues, notably the lymph glands, the bones and joints and the meninges, are the more frequent site of the disease. We still find the teaching that tuberculosis is a generalized disease in children and a localized one in adults. These views are being overthrown by the more recent statistics gathered from more thorough examinations. Wollstein, in a series of 1,131 autopsies on children under 3 years of age (60 per cent. under 1 year), found 185 (16.4 per

cent.) with tuberculosis. She found that 11 per cent. of the children under 1 year of age, 35 per cent. between 1 and 2 years, and 27 per cent. between 2 and 3 years showed evidence of tuberculosis at autopsy. This incidence of tuberculosis found at the postmortem table may appear to some to be high, yet the clinical analyses of all children admitted to hospital wards show a still greater proportion. It is claimed that from 25 to 30 per cent. of all children give evidence of some tuberculous lesion. The further study of these cases has brought out other important points. It has been found that pulmonary lesions of children of all ages are equally important and frequent as the lung diseases of adults. Kossel has found as high as 93 per cent., Adams 90 per cent., and C. Y. White 100 per cent. involvement of lungs and bronchial systems in children with tuberculosis. These figures are interesting when we again remind you that the bovine bacillus has but once been demonstrated in these pulmonary lesions.

Tuberculosis in children under 3 years of age has a striking similarity in all its characters to that found in adults. The pulmonary lesions have their associated secondary processes or sequelae. Cavity formation is found in about one third of the cases, while a caseous involvement of the thoracic lymph glands appears in frequency and distribution not unlike that in older individuals. It is, however, more common to observe the caseous bronchopneumonia in the lungs at this age.

Routine autopsy examinations have been of exceptional value in indicating the distribution,

route of infection and possible portal of entry in the invasion by the tubercle bacillus. Such analyses can be found valuable only when the examinations have been carefully made by a perfected technic and enthusiastic control. Intelligent search must be made by capable hands. I bring these rather obvious points forward because some variations in autopsy findings are due to personal error. With tuberculosis as with many other forms of infection we find that the evidence on which our conclusions concerning the transmission of the infection will be based must be gained through a thorough knowledge of the disease in the human. Animal experiment under apparently natural circumstances or under truly artificial conditions will teach us much in comprehending broad principles of infection, but it must be remembered that the results thus gained have been observed in an animal and that the conclusions apply to that animal and not necessarily to man. Successful experiments on infection in animals may be made to illustrate the possibility of certain modes of invasion. We may demonstrate the direct invasion of bacteria through minute scratches in the skin; the passage of bacteria through the unbroken mucous membranes without leaving a track along their route; the absorption of foreign materials by tonsils or Peyer's patches or the flow of lymph by devious channels from the mesentery to the intrathoracic organs. But, with all this, each of these demonstrations remains an isolated fact proved by animal experiment, but not neces-

sarily forming a correlated story of the manner and mode of infection in man. Hence, again, I must plead for more thorough studies, both pathological and bacteriological, of human material. A few, and the numbers today are gradually increasing, well worked out human cases illustrating the nature of the infecting organism and in as far as possible the sequence of the tuberculous invasion, are infinitely more valuable for a thorough understanding of our human problem than interrupted and isolated facts gleaned in incomparable animal experiments.

In general, one may say that the tuberculous process in children differs in no material respect from the tuberculosis in adults. The pathological change in the tissues are the same in each instance and the manner of attack is also comparable. Bearing in mind, however, that the manner of contact in children differs somewhat from that of the adult, we find that the tissue distribution in certain localities differs in frequency at the two age periods. At the present time, we are not prepared to say that the tissues of the infant differ from the adult in their susceptibility to the tuberculous process. It is not yet definitely shown that the relatively larger proportion of lymphatic tissue in children is more vulnerable to the tuberculous process than in the later years of life. Shennan found, in 1,085 autopsies on children, 413 (37 per cent.) cases of tuberculosis. Of these cases there were 340 in which lymph glands were involved. In 106 cases in which "excavation" of the lungs was found, there were 42 without ul-

ceration of the intestine. It is interesting, however, that in these cases showing pulmonary involvement there were twenty-two without intestinal ulceration having caseous processes in the mesenteric glands. This author believes that a part at least of these glandular infections had arisen from pulmonary infection and hence had developed by invasion through the intestinal wall without producing a recognizable intestinal lesion. Another interesting finding in this series is the presence of a considerable number (eighty-six) of tuberculous ulcers of the intestine in the absence of "excavation" of the lungs. To this the author states: "Even allowing for a large margin of error, there is still a sufficient number left to prove that, in this country at least (Scotland), primary ulceration of the intestine occurs frequently."

On the other hand in a series of 1,432 autopsies on children under 14 years, Comby found tuberculosis in 529 (37 per cent.). Thus the frequency of the occurrence of tuberculosis in early life is the same in Scotland and France. Comby, however, arrives at very different conclusions from those of Shennan. He states that he has never seen a single instance of primary tuberculosis of the intestine and, therefore, places no weight on the initial invasion through the bowel by infected milk. In this series, the glands about the trachea and bronchi appeared to be the most frequent tissues attacked. He concludes that tuberculosis of children is most frequently gained through tuberculous parents or friends by the respiratory tract.

In a series of sixty-two autopsies on children, Dunn found tuberculosis in twenty-five, in twenty-three of which it was the cause of death. The portal of entry was found in twenty-two, twenty times in the lung and twice in the intestine. The remaining three had caseous tuberculous peribronchial lymph glands without abdominal lesions. The intestines were ulcerated nine times, seven of them occurring as secondary infections. The mesenteric lymph nodes were never involved in the absence of intestinal lesions. In the two cases of primary intestinal tuberculosis with caseous mesenteric lymph glands, no intrathoracic tuberculosis was found.

Our own statistics on the incidence and tissue distribution of tuberculosis is based on an analysis of 477 autopsies in which a search for tuberculous foci was made in various parts of the body. It has been our custom to search every case carefully for a tuberculous lesion even in the absence of clinical manifestations or the absence of a lesion in the more common locations. A tuberculous process was met with in 170 cases out of these 477, giving a percentage of 35. As the majority of cases coming to autopsy were adults, there being only twenty-two children out of the total of 477 under the age of 10, these statistics are available for discussion on the dissemination of tuberculosis in adults as compared with children.

ADRENALS

Miliary tuberculosis	3
Obsolescent tuberculosis	4
Obsolete tuberculosis	2

APPENDIX

Tuberculous ulceration 2
Tuberculosis without ulceration 2

BLADDER

Tuberculous ulceration 2
Tuberculous cystitis 5

BONES AND JOINTS

Tuberculous arthritis 2
Tuberculous osteitis 4

BRAIN

Miliary tuberculosis 3
Obsolescent tuberculosis 1
Tuberculoma of cerebellum 1
Tuberculosis of pituitary body 1
Tuberculosis of choroid plexus 2
Tuberculosis of ependyma 4
Tuberculous meningitis 14

BRONCHI

Tuberculous bronchitis 1

EYE

Tuberculous choroiditis 1

HEART

Tuberculous endocarditis 4
Tuberculosis of myocardium 4

SMALL INTESTINE

Tuberculosis without ulceration 3
Tuberculous ulceration 13
Tuberculosis of bowel with perforation 1

LARGE INTESTINE

Tuberculous ulceration of cecum 6
Tuberculous colitis 2
Tuberculous ulceration of colon 14

KIDNEY

Miliary tuberculosis 18
Obsolescent tuberculosis 3
Obsolete tuberculosis 3
Tuberculosis of pelvis 2

LARYNX

Tuberculous ulceration 1

LIVER

Miliary tuberculosis 21
Obsolescent tuberculosis 5
Tuberculoma 3

LYMPHATICS

Miliary tuberculosis of peribronchial glands 6
Miliary tuberculosis of peritracheal glands 1
Miliary tuberculosis of mesenteric glands 2
Obsolescent tuberculosis of peribronchial glands ...48
Obsolescent tuberculosis of peritracheal glands 9
Obsolescent tuberculosis of cervical glands 3
Obsolescent tuberculosis of mediastinal glands 8
Obsolescent tuberculosis of mesenteric glands 20
Obsolescent tuberculosis of omental glands 2
Obsolescent tuberculosis of iliac glands 1
Obsolescent tuberculosis of gastric glands 1
Obsolescent tuberculosis of retroperitoneal glands..12
Obsolete tuberculosis of peribronchial glands 70
Obsolete tuberculosis of peritracheal glands 10
Obsolete tuberculosis of mediastinal glands 2
Obsolete tuberculosis of mesenteric glands 9
Obsolete tuberculosis of retroperitoneal glands 1

LUNGS

Miliary tuberculosis 37
Obsolescent tuberculosis 50
Obsolescent tuberculosis with cavitation 28
Obsolete tuberculosis 54
Caseous pneumonia 7
Caseous bronchopneumonia 4

MOUTH

Tuberculosis of tonsil 1

ESOPHAGUS

Tuberculous ulceration 1

PANCREAS

Miliary tuberculosis 3

PERICARDIUM

Miliary tuberculosis 2
Tuberculous pericarditis 4

PERITONEUM

Miliary tuberculosis 6
Tuberculous peritonitis 10

PLEURA

Miliary tuberculosis	12
Tuberculous pleurisy	5

PROSTATE

Miliary tuberculosis	4
Obsolescent tuberculosis	3

SPLEEN

Miliary tuberculosis	30
Obsolescent tuberculosis	6
Obsolete tuberculosis	40

STOMACH

Tuberculous ulceration	1

THORAX

Tuberculosis of diaphragm	2

THYROID

Miliary tuberculosis	1

TESTES

Obsolescent tuberculosis of epididymus	2
Obsolescent tuberculosis of seminal vesicles	2
Obsolescent tuberculosis of testicle	1

TUBES

Obsolescent tuberculosis	1

UTERUS

Obsolescent tuberculosis	1
Tuberculosis of cervix	1

As is shown in the accompanying table, the tuberculous lesions, on which our figures are based, were either of the acute, subacute or healed type. In making up such tables some difference of opinion may arise as to lesions rightly included in the obsolete group. No great difficulty should present itself in distinguishing the acute and obsolescent variety, but we have observed that some authors suggest a tuberculous basis for fibroses developing in various

organs. The mere presence of heavy plaques of fibrosis in the pleura or elsewhere was not diagnosed as tuberculosis by us unless characteristic histological lesions could be observed microscopically. We have, however, included calcareous glands in the thorax among the number of obsolete tuberculosis. In a similar series of cases and based on a similar method of pathological diagnosis, Adami and McCrae found the incidence of tuberculosis in Montreal at 41.7 per cent. The table gives some interesting figures which in general bear comparison with that found elsewhere. The tuberculous lesions are far more common in the lymph glands than in other tissues. Healed lesions were observed seventy times in the peribronchial glands, ten times in the glands about the trachea and nine times in the glands in the mesentery. Again, caseous or obsolescent tuberculosis occurred forty-eight times in the peribronchial glands, twenty times in the mesenteric and nine times in the peritracheal. Obsolescent tuberculosis was present in the lungs seventy-eight times, in twenty-eight of which there were cavities. Healed pulmonary tuberculosis was recognized fifty-four times, while miliary was seen in thirty-seven cases. It is to be remembered in these cases that a combination of these different forms of tuberculosis was commonly found in the same case so that miliary tuberculosis was not uncommonly associated with a caseous condition in the same lung. Next in order of frequency was miliary tuberculosis of spleen with thirty cases. Miliary tuberculosis

appeared in the liver and kidney twenty-one and eighteen times, respectively.

There is no gainsaying the greater incidence of tuberculosis within the thorax as compared with other parts of the body. This is true for all periods of life even though by selecting a short term of years in early childhood we demonstrate numbers in which apparently a greater frequency of tuberculosis is found in bowel and its appendages. The closer analysis of these periods of life has in recent times indicated that the percentages formerly exploited as showing the greater incidence of abdominal tuberculosis is not correct when an impartial search is given to other parts of the body.

Coming now to our main theme as to the manner in which tuberculosis is acquired in childhood we find that there is no evidence that it differs very markedly from adults. This is even true in the face of the fact that a certain number of children develop a primary intestinal bovine tuberculosis and in consideration of the varying incidence of these lesions in communities where infection of milk is great. If we rule out this mode of infection by a proper treatment of milk there still remains the most important part of our problem in the great proportion of tuberculous children whose disease has been acquired through the respiratory tract. That infection by the alimentary canal is a factor of importance must not be lost sight of and every possible means should be taken to eliminate this source. That, however, our more important problem lies in the disease acquired

by aerogenic means appears clear. Tuberculosis as a disease of childhood is one having to do with the pulmonary system. The fact that the statistics up to the present show that the bovine bacillus is almost never the infecting agent of the lung is evidence that we can lay no stress whatever upon the generalized tuberculosis arising from the bowel. Criticism which may be brought to bear upon the statement that the oldest lesion is so commonly found in the peribronchial glands, is insufficient reason, when theory alone is offered to supplant these definite findings. Admitting that the tubercle bacillus may pass through mucous membranes without leaving a mark at the point of entrance we must, in an endeavor to follow its subsequent routes, show the pathway along which it has traveled and left unmistakable signs.

The route of travel by the tubercle bacillus is readily defined within the thorax. The passage of micro-organisms and inert particles can be demonstrated from the lumina of bronchi, bronchioles and pulmonary alveoli. The entrance into the lymphatic stream and their carriage by phagocytic cells may be readily demonstrated in man and animals. The development of the characteristic lesion and the process of caseation can be easily followed through the various stages. The subsequent dissemination by the blood stream to the lungs and distant organs no longer forms a mystery in the study.

Of primary infection of the tonsils we have little to say. That it may occur is obvious, but in our own experience it is more usually a

secondary infection from the lungs. Nevertheless infected tonsils whether primary or secondary may give rise to tuberculous processes in the neighboring superficial lymph glands. An interesting finding having some bearing upon cervical adenitis is observed in the advance of the tuberculous process from one gland to another. It is not uncommon to find a chain of peritracheal lymph glands, involved in tuberculosis, extending from an old caseous process in the lymph glands at the bifurcation. In these instances, and they are the usual, the most marked involvement is in the lowermost intrathoracic group while a lesser and diminishing process is found in the successive glands as we advance upwards along the trachea. I do not think that there is any direct association between these deep peritracheal and the superficial groups. The converse of this is also true, that is where the tuberculous cervical adenitis has begun from infected tonsils there may be a localized infection of the superficial group, but rarely if ever do we find a direct lymphogenous transference into the thorax and lungs. It is of course to be remembered that a tuberculous process in any portion of the body may give rise to a disseminated hematogenous tuberculosis.

Thus broadly in children as in adults the intrathoracic tuberculosis bears a much greater importance as the primary seat of infection as well as the severity of the induced disease process. The child acquires this tuberculous process by droplet infection through the respiratory

tract. It is not uncommon that the intrathoracic lymph glands are involved early and dissemination to other organs takes place from these structures. An alimentary infection probably occurs more commonly in children than in adults but has no great significance in the subsequent development of pulmonary tuberculosis. Other portals of entry, as the skin, mouth, tonsils, nose and genitalia, play little or no part in bringing about other than localized lesions, and the discussion of them should not confuse the issue of the broader problem of tuberculosis.

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Chronic Interstitial Nephritis and Arteriosclerosis

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CHRONIC INTERSTITIAL NEPHRITIS AND ARTERIOSCLEROSIS.

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No agreement has as yet been reached as to the nature of and the progressive changes leading up to the granular kidney. Almost all the factors having to do with the carrying out of the normal kidney function, as well as the known factors giving rise to processes of fibrosis in other organs, have been mentioned as the inciting cause of renal sclerosis. Particular weight has been placed upon certain of these factors, because of their presence during one stage of the disease; but the opportunity of weighing their importance as an active cause for the contracted kidney has not been sufficiently good to direct a knowing finger at them. No one has yet been able to describe in a single instance the sequence of events from the beginning to the fully developed chronic interstitial nephritis. Thus, opportunity has remained open for wide speculation on the interpretation of the pathological processes involved.

Some attempt has been made to link up the clinical and urinary findings with the successive changes that are taking place in the tissues of the kidney. These, however, have added little to our understanding of the process. True it is, that with the fully developed disease, certain manifestations make their appearance, and we believe that some light has been thrown upon the correlation of the urinary character with the altered functional capacity due to renal sclerosis. But as for saying that the clinical manifestations bear any relation to the structural change of the kidney prior to the stage of granular contraction or, better, that we can forecast the outcome or even suggest the past processes in the kidney by clinical analyses we have no definite evidence.

Thus the problem has been left in the realms of conjecture and in the absence of incontestable proof by experiment, our knowledge concerning the development of the granular kidney has not materially advanced since the days of Gull and Sutton. In the face of

this we do not wish to minimize the value of the many observations which have given us a clearer understanding of some of the finer reactions in the kidney substance; but it would appear that the minutiæ of some of these observations have led us astray from the broad aspects of the problem. That Jores should find a splitting of the internal elastic lamina of the renal arterioles, and from this finding discuss the importance of those still indefinite factors inducing arteriosclerosis as of prime importance for kidney disease, is, it seems to me, quite aside from the main issue.

For the main part, as was brought before the Association of American Physicians last year, studies upon the pathological nature of chronic interstitial nephritis have been made upon the advanced form of the disease. The criterion for the recognition of the important type of the disease is still based upon the description of the kidney as given by Richard Bright. If we adhere closely to these described characters, we will find there is a general similarity grouping them into one class. Gradually, however, our attention has been drawn to the fact that there are other forms of renal sclerosis, differing to a greater or less degree from the type here under discussion and readily recognized by careful observation and supplemented by the microscope. Thus we have kidney fibroses associated with hydronephrosis, ascending infection of ureter and bladder, hematogenous infection (pyogenic), infarcts, thromboses, amyloid disease, syphilis and other infective granulomata, and arteriosclerosis. But when we are speaking of the small, contracted or granular kidney we have in mind a diseased condition of the kidney which is different from each of these. It is different not only in the structural changes induced, but it is different also in its progress and in the distant systemic responses. The small, granular kidney is recognized by its small size, the thickening of its capsule with adherence to the underlying cortex. The kidney substance when stripped of its capsule is distinctly granular, each granule being surrounded by a depression from which fibrous tissue radiates parallel with the ascending vessels. The kidney substance may appear red, but, on the other hand, may be quite pale with not a few of its granules as yellow as the adrenal cortex. The cortex is most markedly altered, and is commonly only half the thickness of the normal structure. Within it are found many fine wedge-like sclerotic areas which occupy the positions between the granules observed on the surface. Alternating with these areas of fibrosis a fairly normal kidney tissue is observed. Along the patch of these radiating fibroses the tubules and Malpighian corpuscles become involved. The medulla is less altered, although a hyaline fibrosis not infrequently surrounds the excretory tubules. As in other regions subject to progressive fibrosis a considerable adipose tissue develops in the surrounding structures, particularly about the pelvis.

At the present time, opinion as to the development of this form

of the interstitial nephritis has been divided mainly between two schools: the one considers it the outcome of a low grade but progressive inflammation, while the other believes it the result of a primary circulatory disturbance with a secondary atrophy and replacement fibrosis. Unfortunately the issue has been somewhat confused by the further introduction of the terms primary and secondary interstitial nephritis. Each group claims that their explanation is adequate for the so-called genuine contracted kidney. We would do well to drop such irrelevant terms and leave the application of a new nomenclature to him who clearly indicates the pathological sequence of events concerned in chronic interstitial nephritis.

Gull and Sutton considered the relationship of the arteries to the diseases of the kidneys as a peculiarly intimate one in which the arterial processes preceded and determined the interstitial nephritis. No agreement was reached by subsequent workers of the actual nature of the arterial disease, some viewing it as an endarteritis (Thoma), others as an hypertrophy (Johnson, Ewald, Friedmann), while the subsequent work by Prym and Jores drew attention to the arterial lesion as a true arteriosclerosis. Jores, furthermore, contended that the associated arterial changes in other organs, as was described by many, was also an arteriosclerotic process. The differentiation of this process rested upon the finding of deep arterial degenerations associated with a splitting of the internal elastic layer. As Jores, however, observed, arteriosclerosis may occur in the arteries of other organs in the absence of sclerosis of the renal vessels.

While the above authors were contending the dependence of chronic nephritis upon disease of the bloodvessels, Ziegler maintained the differentiation of types of chronic nephritis into groups associated or unassociated with arteriosclerosis. Those kidney lesions resulting from arteriosclerosis he believed to be individual and of a purely degenerative character, and designated them the arteriosclerotic kidney.

Both Jores and his pupils repeatedly remarked that chronic interstitial nephritis is a disease most frequently encountered in advanced life, a period when arteriosclerosis is also most prevalent. Nevertheless, they remark upon the finding of occasional cases in which they have been able to demonstrate advanced renal sclerosis unaccompanied by arteriosclerosis within the kidney. This agrees with the finding of Orth, who believes that in chronic interstitial nephritis the vascular changes are not essential because their variety does not correspond with the extent of the lesions. Roth described a number of cases in which renal sclerosis was advanced, but in which the arteries did not show the type of sclerosis defined by Jores as arteriosclerosis. He did, however, find that the arteries were affected by a connective-tissue thickening of the intima with

splitting of the elastic lamina. As, however, processes of degeneration were wanting, he refused to call it arteriosclerosis. He suggests that these vessels might subsequently show arteriosclerotic change. From his observations we can only conclude that the kidney lesions have advanced with greater rapidity than those in the intima of the renal vessels, and his cases illustrate the point we wish to make that the narrowly defined form of arteriosclerosis as given Jores is not an essential factor in bringing out subsequent interstitial nephritis.

Roth described 3 cases of chronic interstitial nephritis without arteriosclerosis. In the kidneys, however, endarteritis was present in the small arteries. The cases were of relatively young individuals, and all of them had definite chronic or recurrent heart and arterial diseases. Yet with it all neither Jores nor his pupil sees any direct relationship insofar as a common causative factor is concerned in the simultaneous and progressive lesions in these three organs. These authors lay much stress on the finding of a single sclerosed arteriole or the mildest beginning of intimal degeneration as indicative of the influence of arteriosclerosis upon the kidney. No recognition is given to the fact expressed in their own cases that the fibrosis of the kidney was markedly advanced, and in the late stages of contraction, while the arteriosclerosis was only beginning. We can in no way follow the conclusion of this author as illustrated by his own cases that the chronic interstitial nephritis was the result of the early endarteritis demonstrated.

In the admirable work of Councilman (1897) the part played by the inflammatory process in bringing about the interstitial lesions of the cortex of the kidney was well demonstrated. In part, the cases studied included some of scarlet fever, diphtheria, pneumonia, and other infections, and the lesions described were of the nature of diffuse non-suppurative interstitial nephritis or types of glomerulonephritis. Of the latter, two forms were distinguished: a non-suppurative exudative form and a proliferative type. No clear distinction can be made between the etiological factors present in these two types, and it would seem that both may arise from the same causative factor. At the time of carrying out his work, bacteriological methods were not available to make a distinction between the various forms of streptococci, and we find the author speaking of the organisms isolated from cases of heart disease as pneumococci. I believe we will be correct in interpreting these results as indicating the presence of the Streptococcus viridans group. These organisms were found in cases of glomerulonephritis in large percentage, but the author's descriptions of the lesions indicate a transition between the glomerulonephritis and the diffuse, interstitial type. The work of Wagner bears out these findings, particularly in indicating the importance of the inflammatory process of scarlet fever and other infections in bringing about permanent interstitial change.

The work of Councilman is among the few in which a study of the progressive lesions of the kidney was accompanied by bacteriological examination. Of this he says: "Various forms of disease of other organs, particularly of the heart, are often associated with them, and bacteriological investigation has frequently shown in many cases the presence of certain organisms in the kidneys. In most cases the bacteria are found in some other lesion and in the blood, and their presence in the kidneys is but a part of a general septicemia. Moreover, the same conditions in the kidneys may be found associated with various organisms, and the same organisms may be associated with widely different anatomical lesions." A very fertile field awaits the routine study of the bacteriology of the kidneys in conjunction with the histological examination of all types of infection. The work which has been performed up to the present time is very suggestive of indicating the actual presence of bacteria rather than their toxins in the interstitial response of the kidney.

Undoubtedly what appears as complete disagreement in the personal observations on chronic nephritis lies mainly in the methods and material studied. Although the anatomical classification of kidney disease has not found favor with either the clinician or the pathologist, yet in the absence of a better substitute we all revert to this method. Müller attempted an etiological classification which as yet is hardly practical, and Herrick, while finding the old anatomical grouping unsatisfactory, offers nothing to replace it.

The types of nephritis which today attract our attention as the forerunners of the contracted kidney are the acute glomerulonephritis and the acute non-suppurative interstitial nephritis. Without desiring to describe the various types of glomerulonephritis, as well as the variety of interesting lesions that may be observed in the Malpighian body and Bowman's capsule, there is ample evidence that, in the human, these glomerulonephritides are infective lesions (Councilman, Gaskell, Baehr). The important feature lies in the fact that the glomeruli become the centres of inflammatory response in which a non-suppurative exudate and endothelial proliferation of the capillaries and a proliferative response of the inner lining of the capsule is commonly observed. The occlusion of the capillaries of the glomerulus by cellular proliferation or by thrombosis is only an added complication, and the subsequent degeneration that occurs in the tubules of the kidney is also to be viewed as a secondary disturbance depending upon vascular change rather than an injury produced by the primary factor.

A study of these cases of glomerulonephritis soon convinces one of the varying picture, even during the acute stage. In some thromboses of the glomeruli are common, in others rare, or the lymphocytic infiltration of the glomerulus is great and confined to this structure; others again, show the inflammatory reaction diffuse,

surrounding Bowman's capsule, infiltrating the stroma between the tubules and following the course of the interlobular arteries and vessels of the intermediate zone. Many such cases have been described, by Councilman, Ziegler, and others. In fact, the picture presented by those kidneys in which the inflammation is more diffuse simulates more closely the type of acute interstitial non-suppurative nephritis. This latter type, which was originally discussed as a disease of the kidneys found after scarlet fever, measles, and sometimes smallpox, is now being incorporated with the glomerulonephritis, mainly because a certain amount of glomerular disturbance is always present. Fahr finds the streptococcus and pneumococcus most frequently associated with acute interstitial nephritis, and finds also that the same organisms are the chief cause of glomerulonephritis.

In short, although there are variations of glomerular lesions, and we encounter forms of inflammation of the kidney stroma, there does not appear to be any difference in the causative agent, most frequently the Streptococcus viridans. We must, however, point out that the bacterial infection reaches the kidney under different circumstances, and in a somewhat different form, in the various systemic diseases in which it is met. It is the bacterial clusters or small infective thrombotic masses which are liberated in heart disease that give rise to a type of glomerular infarction. In this way particular structures in the kidney are more intensely involved than others. So, too, in cases of bacteriemia, by organisms of low virulence, the kidney, as well as other organs, becomes a local focus of infection and this is particularly true in the bacteriemia of acute rheumatic fever in which the heart and bloodvessels are also affected. In these infections the heart may be involved in a variety of ways, and when the endocarditis becomes well-marked the kidney may be subject to embolic processes in its glomeruli, so that both the acute interstitial and the glomerulonephritis are simultaneously prominent. Hence it is obvious that to state that a definite type of kidney lesion is constantly to be found as a disease associated with infection of other organs is only voicing a rule with prominent exceptions.

The frequency with which acute interstitial and glomerulonephritis are present with infective heart disease is known to all who have observed these cases at autopsy and studied the tissues. It is, furthermore, easy to demonstrate the fate of the early inflammatory process. Fibroses of the glomeruli, of Bowman's capsules, and of the intertubular stroma may be demonstrated in all stages of formation, and recurrent attacks of these infective processes give rise to combinations of inflammatory responses in the kidney tissues. The question immediately arises whether the localization of these inflammatory processes gives us definite types whereby their future scars may be recognized. In answer to this the best reference

is made to a few experimental results. In these it has been shown that inflammatory reactions in the kidney due to bacterial agents are prone to follow and surround the course of the bloodvessels particularly the interlobular vessels, and the ascending cortical branches as well as the afferent arteries of the glomeruli. Associated with these inflammatory responses there are not infrequently glomerular reactions, infiltrative, proliferative, or thrombotic. The progress of these lesions is similar to that in the human kidney and the end-result is a process of fibrosis radiating in its character with shrinking and granulation of the cortex and contraction of the entire kidney. Such lesions were reproduced in animals by the use of organisms (various members of the Streptococcus viridans group) isolated from infective heart disease, and the responses in the kidney were found to be accompanied by a myocarditis, at times an endocarditis, and in a few cases pericarditis. In only a few instances were systemic intimal arterial lesions obtained, although the perivascular response was always noted. Here, then, we have evidence of the development of the various stages of the contracted kidney in the presence of chronic infection and in the absence of primary arterial lesions.

These findings are in accord with the observations on human material and explain the occurrence of the contracted kidney in the first half of life as well as its greater frequency in the later years. Like all chronic diseases, the frequency of chronic interstitial nephritis is greatest in the late decades, and it is also a rather depressing outlook when we find that the incidence of these chronic diseases shall increase with the saving of more lives in childhood from death from scarlet fever, acute rheumatic fever, chorea, and other Streptococcus viridans infection. We must also equally appreciate that the heart and arteries suffer, sometimes much, at other times less, by invasion of these bacteria. In the arteries an endarteritis, a mesarteritis, and a periarteritis have all been repeatedly demonstrated in these infections during the early years of life. Of the heart lesions, we need make no other comment than reference to Aschoff's studies upon focal myocarditis, and of the frequent presence of endocarditis in the human and in experimental infections.

What, then, is the relation of renal arteriosclerosis to chronic interstitial nephritis? Before one can answer this we must have a clear understanding of the nature and genesis of arteriosclerosis. It is not enough to boldly speak of general arteriosclerosis as of common type and constant origin. Nor is this true within the kidney itself. There are arterial lesions within the kidney whose origin is widely different and which vary in their character.

Ziegler has long ago demonstrated the peculiar renal fibrosis resulting from peripheral arteriosclerosis. In old age, where it is not uncommon to have various arterial tracts severely involved in

sclerosis and in which the lumina of the vessels are distinctly impeded, atrophic changes result in the area supplied. It is obvious that the amount of sclerosis varies greatly and is bound to pick out limited areas. The kidney tissues which suffer from the circulatory disturbances undergo atrophy, and even complete loss, without, however, necessarily showing evidence of intracellular degeneration (fat), as is otherwise so commonly encountered. The kidney shows areas of sharp depressions scattered irregularly over its surface so that its structure and shape are distorted. The individual depressions simulate those of infarct, but microscopically may at times be distinguished from these in that the involved areas contain some of the parenchymatous structures not completely destroyed. Furthermore, the kidney capsule is rarely adherent and the cortical surface between the areas of depression is relatively smooth.

Such depressions are the result of the obliteration of fairly large vessels within the kidney. At times, it may be, smaller vessels involving more restricted portions of the kidney are affected. This, then, leads to a local fibrosis of the glomeruli supplied by this circulation. Under these conditions the process, both in the glomeruli and tubules, is one of slow and progressive degeneration, with a secondary replacement fibrosis. It is unusual to observe under these conditions any evidence of an inflammatory reaction.

Compared with the granular contracted kidney, these changes in the arteriosclerotic kidney are quite different. It is inconceivable that a process of arteriosclerosis could so uniformly affect so many arterioles of a constant caliber to give the character found in the uniformly granular kidney. A comparable picture is to be observed in no part of the body, and we are well aware how uncertain is the distribution of arteriosclerosis. As the fibrosis following upon processes of degeneration in the atrophies of vascular scleroses is without inflammatory response, one misses entirely the presence of a granulation tissue and subsequent adhesions. The absence of these is noted in the freedom of the kidney capsule and in the lack of synechiæ about the glomerulus. Frequently, too, Bowman's capsule shows no thickening. Ziegler truly calls this the senile kidney.

It is, however, not common to meet with a clear-cut and uncomplicated case. The vascular scleroses of the kidney are most commonly the result of the same influence which has produced a primary inflammatory lesion in the kidney stroma. Hence, the development of scar tissue in the renal structures goes hand in hand with renal arteriosclerosis. Here, however, in the early stage, as well as during the years of progressive involvement, the kidney tissue and arteries show the presence of inflammation. These inflammatory deposits are easily recognized, and obviously vary in amount at the different stages. Jores has seen them in his inter-

stitial nephritis, but has taken the view that no relation between the arterial disease and the inflammation can be determined. Like the results of the Streptococcus viridans infection upon the heart, giving rise to inflammatory processes differently disposed, so, too, this same infection, which is so frequently at the bottom of the fibrosis of the contracted kidney, brings about inflammatory reactions of varying intensity in different portions of its structure. The arteries appear to form the centre of distribution for these reactions, and much of the response is spent in the tissue surrounding the small vessels coursing through the cortex. To a certain extent, however, intimal reactions are also found. The latter, however, arise somewhat later in the course of the kidney disease, so that examples are not difficult to demonstrate in which intimal sclerosis is wanting while a non-suppurative inflammation is active about the vessel. Later, however, the picture is reversed and the intimal sclerosis attracts our eye. This is now the stage when appearances suggest that a close relation of cause and effect exists between the intimal arteriosclerosis and the renal fibrosis.

The intimal disease of the arteries most commonly met with in the late stages of chronic interstitial nephritis consists of a chronic endarteritis with deep, fatty change. The presence of a true hyperplasia of the musculo-elastic layer with secondary degeneration of the inner muscle bundle has never been met with by us, nor have its advocates ever clearly demonstrated its presence. The finding of splitting of the internal elastic lamina is now found to have no specific bearing on the problem of arteriosclerosis. McMeans (of our laboratory) has shown that such splitting is the common occurrence during inflammatory reactions of the intima.

Granted, therefore, that the early reactions which lead to the granular contracted kidney, simultaneously involve portions of the kidney parenchyma and its arteries, it is often extremely difficult to distinguish in the late stages of the disease exactly how much of the scar tissue has resulted through inflammation or as replacement fibrosis following arteriosclerotic atrophy. We should, however, continue to distinguish clearly the arteriosclerotic kidney of Ziegler from the granular interstitial nephritis, the former giving rise to true atrophic processes in the parenchyma with replacement fibrosis, the latter having an inflammatory basis for the development of connective tissue variously distributed about the important structures of the organ.

THE INFLUENCE OF INTRAVENOUS INOCULATIONS OF CHOLESTERIN UPON BLOOD CELLS

By OSCAR KLOTZ and MARY W. SPENCER

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The influence of intravenous inoculations of cholesterin upon blood cells.

By Oskar Klotz and Mary W. Spencer.

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Some years ago (1907) Talquist believed that he had found the harmful substance present in the *Bothriocephalus latus* leading to progressive anemia. The substance which he isolated from these worms was a cholesterinester present in greatest proportion as cholesterin oleate. He found that a synthetic cholesterin oleate did not have such active hemolyzing properties as the extracts from the worm, but on his general findings he believed that this substance was the cause of the anemia and suggested the possibility of other anemias arising through the action of similar substances. Since this time cholesterin in various forms has been used to a considerable extent for other experimental purposes. In some of these experiments the materials were fed to animals while in others they were introduced by inoculation. Depending upon the dosage there was a variable increase in the cholesterin content of the blood. This cholesterin was present in combination with fats or lipoids. Even with the development of a continued hypercholesterinemia amounting to several times the normal blood content, none of the authors have remarked upon the production of a progressive anemia. In our own feeding experiments no anemia was apparent, although the cholesterin of the blood was often very high.

Recently we have studied the effect of the direct introduction of cholesterin combinations into the blood. An emulsion of a cholesterin combination with sodium oleate, containing 7.5 per cent. of cholesterin and 5 per cent. of sodium oleate, was used. The cholesterin in these materials forms a combination with sodium

oleate so that colloid globules remain in suspension and are readily introduced into the circulation of animals. The cholesterin in this form does not give rise to a foreign body reaction as when the pure cholesterin is used. Furthermore, this mixture does not show the active hemolysis in the test tube, as is demonstrated by the same quantities of sodium oleate.

Two rabbits were treated every second day by intravenous inoculation of 2 c.c. of the emulsion for a period of two weeks, while a third received from ½ to 1 c.c. during a similar period. Counts were made prior to the initial inoculation to determine the normal for each animal. Counts were also continued for ten days after the last treatment. In none of the animals were we able to observe any effect of the inoculated material upon the red blood cells. In the normal rabbit we have found a fluctuation between six and seven and a half million red cells and at no time in the experiments was there any appreciable decrease below the normal minimum. There was no alteration in the morphology or staining qualities of the red cells. Furthermore, it was found that but slight reactions occurred in the white cells of the blood. Immediately following the inoculation there was a temporary rise in the number of white cells amounting in its greatest extent to 2,000 cells above the normal maximum (10,000). This increase remained only for twenty-four hours and then the count declined to normal. The increase was not confined to any particular type of cell, though the response in the polymorphonuclear neutrophiles was more common. The experiments indicate that for the amount of the cholesterin mixture used intravenously, there is no particular reaction in the blood cells of this animal. There was no evidence that the cholesterin macrophages appearing in organ lesions during hypercholesterinemia, migrate by the blood stream.

The Invasive Quality of the Streptococci in the Living Animal

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THE INVASIVE QUALITY OF THE STREPTOCOCCI IN THE LIVING ANIMAL.[1]

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Invasion, virulence, and pathogenicity as well as resistance and susceptibility are all relative terms and must be considered from the point of view of the animal body as well as the bacteria themselves. This is generally recognized but is not constantly remembered.

The streptococci have primarily high invasive powers. By this I mean that they are capable of entering the animal body under a wide variety of conditions. It is only within the last few years that this has been broadly recognized. The Bacillus coli formerly was the organism found as the chief secondary invader. In autopsy bacteriology the colon bacillus is frequently reported as the common bacterium invading after death, and in studies of peritoneal and other fluids the same organism was found practically to the exclusion of all others. More careful technic has, however, definitely shown that streptococci of various types invade the tissues and body fluids long before the colon bacillus, and are, moreover, almost always present where the latter is found. A long series of blood cultures taken by workers in our laboratories from the arm vein immediately or shortly after death, as well as numerous cases reported in the literature, serve to demonstrate this fact. Numerous investigators have further shown that this invasion by streptococci is more commonly antemortem and often occurs as the so-called agonal infection.

From these cases illustrating the invasive power of the streptococci under definite recognizable conditions of damaged resistance we are able to follow a graded series of cases in which invasion took place hours, weeks, months, and years before death as also innumerable examples when death did not result from the invasion. Many

[1] Read before the American Association of Pathologists and Bacteriologists, Washington, May 10, 1916.

investigators believe that streptococci are frequently invading the body, but that under conditions of relatively good health they are being continually destroyed.

It is certainly true that streptococci invade the blood stream more often than most other bacteria. Their demonstration is not always easy, as they frequently only temporarily invade the blood. It is not uncommon to find that 10 c.c. of blood fails to reveal the organisms while 15 c.c., 20 c.c., or 25 c.c. may be required to demonstrate a single colony. We are limited, for obvious reasons, in the amount of blood we can take, and therefore we endeavor to choose a time when the number of bacteria in the blood is greatest. There is no royal road to successful blood cultures in many of these cases. Serum broth with or without carbohydrates is probably the best medium and by adding a tube of melted agar, anaërobic cultures are readily made. In this as in many similar tests a positive result is important; a negative leaves the question open. There is ample evidence to show that streptococci found in various lesions of the body have probably been distributed by the blood stream, but the invasion from the nearest naturally infected parts of the body must always be first considered.

The portals of entry for streptococci are wide-spread and do not play as important a role in the invasion as is the case with other bacterial groups. The organisms may enter the body from the mucous membranes of the throat, that of the intestinal tract, the uterus, from the skin, and many other points. Naturally, the conditions will vary somewhat according to the types of tissue encountered by the organisms. Whether they further increase in numbers and bring about damage depends largely upon the relative susceptibility or resistance of the different tissues of the body; that is, the environmental conditions they encounter. I do not assume there is a specificity on the part of the streptococci as to what tissue or organ they attack, but, granted that the natural distribution plays no part, I am convinced that they locate in whatever areas offer the proper conditions of relative susceptibility. No two animals offer the same conditions for the invasion of bacteria nor identical susceptibility or resistance in all their tissues. It is true, no doubt, that a group of animals or human beings living under the same conditions will tend, more or less, to similar tissue susceptibilities, and that at different seasons of the year alterations in temperature and moisture of the air, changes in food and ventilation, and number of other environmental conditions will tend to alter these susceptibilities in the entire group. Nevertheless, certain individual differences will still persist. Many experiments on animals demonstrate this variability in tissue susceptibility in different groups of the same race of animals. Everyone is familiar with family susceptibility as well as individual variations following the same infection. These facts are often

forgotten when animals are used in the study of bacteria, but being remembered will often prevent misinterpretation of results.

By virulence of the streptococci I mean something further than invasive power. Virulence is the ability of bacteria to multiply in the tissues, to resist the defensive mechanism, to increase the susceptibility (probably by toxins) of the tissues, and to prepare the way for the manifestations of pathogenicity. If the virulence is high the incubation period is reduced and the pathogenic characters are seen early. It is relatively common in infections with hemolytic streptococci to have a slight local reaction at the portal of entry. The virulence in these cases is very intense and the resistance is rapidly overcome.

Three groups of streptococci have been arranged as follows: (1) Those lacking in invasive, virulent, and pathogenic qualities; these include the strictly saprophytic forms, which I believe are very rare. (2) Those with well-developed, slowly acting virulence (possibly on account of a similarity of metabolic activity to that of the host) but with definite and eventually, when the infection continues, severe pathogenic powers; in this group we have the Streptococcus viridans organisms. (3) Those with powerful invasive power, active virulence setting up violent defensive reactions and exhibiting a high pathogenicity. Under these we have the hemolytic streptococci.

There are a number of conditions that modify the demonstration of these qualities. The portal of entry may be more or less favorable to a rapid manifestation of all these characters. Locally, highly resistant tissues may check either the invasion, the further growth of the bacteria (virulence), or the pathogenicity, while other tissues offer more favorable conditions, particularly mucous membranes in which disease processes, set up by the invading organisms or other bacteria, may offer a ready entrance for the bacteria to underlying structures or the general circulation. The number of bacteria invading the body will also greatly influence the virulence and the pathogenicity. This is particularly to be remembered in consideration of invasion from primary infected foci such as are found in the tonsils, gums, intestinal tract, uterus, and other parts. These local foci also serve as points in which the bacteria may fully develop their invasive, virulent, and pathogenic characters. They serve, as it were, as training grounds for the bacteria. The increase in these qualities is within fairly narrow limits. The hemolytic streptococci, which are the strains capable of becoming highly virulent and pathogenic, may here not only increase in numbers but develop more rapidly these qualities. The members of the Streptococcus viridans group may also have the opportunity in these foci of increasing in their characters, but only within the limits of the group, and at no time do they develop the type of virulence and pathogenicity found in the streptococcus hemolyticus group.

There is another condition found in these foci which has led to much confusion among early investigators, and that is the presence in them of a mixture of bacteria. Such foci develop as the result of a lowering of resistance in the local tissues and the invasion of bacteria of the grade of virulence proportionate to the condition. Following this several things may happen: the bacteria may increase in disease-producing power within their capabilities or they may prepare the way for more vigorous types of organisms, the two or more growing commensally or until the weaker succumbs. At any time during this process a further invasion of tissue or the blood stream may occur by the original organisms, the mixture, the dominant organisms in the mixture, or by the surviving strains. In any case the organisms invading the body will either be overcome or will cause secondary foci in those tissues in which the environment resulting from the noxious influence of manifold agencies including toxins is favorable for their development.

These possibilities which I have cited are what actually occur. We find infected foci with one type of streptococcus or with two or several types as well as with other bacteria. We can frequently demonstrate the entrance of a new type and its survival in various stages of the process. When the blood stream is invaded it is most commonly by one organism, but by no means infrequently by two. This blood stream invasion is mostly transitory, but sufficient to give rise to secondary foci from which corresponding types of organisms may be recovered. Furthermore, these secondary foci may serve as new distributing points. Wrong interpretations of these findings have led to most astonishing "biological alterations and mutations."

What appears to be the obvious focus of infection is not always the source from which invasion actually occurs. An inflammatory process of the intestinal tract synchronous with pyorrhea, for example, may be the condition leading to the invasion of bacteria. It is, indeed, often extremely difficult to be certain of the conditions present, and we should be very careful in drawing dogmatic conclusions from our necessarily limited findings.

There are certain states of lowered resistance that appear to be favorable for the invasion and activity of one or other of the two main streptococcus groups. In the puerperal state and in scarlet fever the conditions usually favor an infection by the hemolytic streptococci while chronic irritations, such as are found in the stomach, kidneys, and other organs from a variety of causes, general lack of tone following sedentary life, exposure to cold and dampness, and many other similar, often temporary, lowerings of resistance offer conditions most suited to the attack of the non-hemolytic streptococci. In perforations of the intestinal tract in which the non-hemolytic strains are numerically greatly in excess of the hemolytic, judging from cultures of the intestinal contents, it

is usually the latter which survive and cause the severe results, which means that the hemolytic forms can withstand the active defenses of the body better than the non-hemolytic; in other words, they are more virulent.

The members of the hemolytic streptococcus group include the strains with the highest virulence and pathogenicity. They are the causative agents in the most severe types of streptococcal disease, such as severe septicemia, erysipelas, peritonitis, and other pyogenic infections. These infections give severe local or general reactions and are often fatal, but even with recovery we have the clinical picture of severe acute disease.

The streptococci of the viridans group, on the other hand, are the common cause of chronic infections. They have high invasive power and attack tissues in a state of lowered resistance, stimulate little reaction on the part of the body, apparently render the tissues more susceptible to reinfections, and death, if it occurs, only follows after a prolonged course or repeated reinfections. Clinically these cases are characterized by a relatively mild and chronic course with frequent exacerbations. Occasionally a Streptococcus viridans strain prepares the way for a hemolytic strain and the disease becomes a more severe one, and in cases recovering from a hemolytic streptococcus infection an invasion may occur with one of the non-hemolytic forms.

A proper classification is necessary to enable us to recognize the various varieties of streptococci. The method which I have been following for some time and which is published this year has enabled me to greatly enlarge my views on the invasive and other qualities of the streptococci. I have been able to recognize mixtures of different streptococci belonging to both of the two main groups and to trace the source of the invasion in many cases. There is one important point which has been noted in this study, and that is that the streptococci are not specific in their disease production. There is no evidence to support the view that only one type of streptococcus produces endocarditis or nephritis or gives rise to septicemia in the puerperium, scarlet fever, or other conditions of lower resistance. Neither do I believe that one streptococcus is responsible for all the ill effects in all of these cases. Streptococci of several kinds live in symbiosis in the mouth and the intestinal tract. They are often found in mixtures in other infected areas as in the peritoneal, pleural, and other cavities. The blood stream may be invaded by more than one type, although, as a rule, we only recover one. It is, therefore, not surprising to find different organisms locating in various damaged areas. Under these conditions by the use of the hemolytic test alone we are liable to draw erroneous conclusions. Thus by this single method, without the carbohydrate fermentation tests, the various members of the viridans or hemolytic groups cannot be distinguished.

There are many interesting points for discussion in tracing the source of many of the streptococci. The streptococcic flora of the mouth has always been confusing. The finding of mouth streptococci in the air of rooms as shown by Gordon may be taken as indicating pollution of the air from the oral cavity and thus the flora of the mouth is continually being replenished from the mouths of others. Another source of origin for these streptococci appears to be cows' milk which in turn is subject to contamination from the cows' feces while still a third source is the air streptococcus derived from horse manure. In the mouth cavity many of these strains find favorable conditions for further development. Broadhurst has shown that many streptococci, being swallowed in the sputum, can pass through the stomach without being destroyed in the limited time by the gastric juices. In the intestinal tract the cultural conditions are markedly different from those of the mouth, and many of these strains are destroyed, while others, especially the more vigorous forms, such as Streptococcus fecalis and Streptococcus equinus, flourish and produce a flora quite different from that found in the mouth.

It cannot be too often repeated, however, that the entire flora of any region of the body may be suddenly changed by alterations in the food supplied to the bacteria, the reactions of the secretions, the presence of inflammation, and many other important environmental changes. Particular streptococci finding these new conditions favorable, multiply rapidly and the former inhabitants are crowded out. In diphtheria, for example, streptococci may greatly increase in numbers and seriously complicate the conditions, as has been repeatedly pointed out by Le Gros and others. Although the streptococci present in the greatest numbers in normal saliva and intestines are of the viridans group, a careful search will almost always reveal members of the hemolytic group, and these, as experience teaches, are the strains most capable of producing severe infections. In this connection the influx of strains from disease sources outside of the body, in which the streptococci have developed to a high degree, their disease-producing characters must not be forgotten.

It is beside the point to argue that streptococcus infection in rheumatism and other diseases is a secondary invasion. It is most certainly true that in practically all our infections the bacterial attack is secondary to the necessary conditions of lowered resistance. In many of these arguments one is reminded of Pettenkofer's demonstration to prove that the cholera vibrio does not always cause epidemics of cholera.

The condition of lowered resistance in the Streptococcus viridans infections are receiving much attention but we are only on the threshold of this study. When the streptococci have established themselves within the system we are usually at a relatively late stage

of the disease. Libman has shown that in viridans endocarditis the cases may become spontaneously bacteria-free. The work of many of the German workers would indicate, though on somewhat dubious grounds, that the viridans endocarditis is almost always eventually fatal. There is no doubt that with more careful blood cultures the frequency of viridans infection in the earliest stages is being shown and the recurrent attacks are being guarded against (Oille, Graham, and Detweiler).

Spontaneous streptococcus infections in animals is a frequent occurrence. I have isolated streptococci from about half of 200 guinea-pigs infected spontaneously. In most of these the streptococcus infection was the cause of death, but in others the streptococci were definitely secondary invaders during the course of other infections. In certain animals dying of a hemolytic streptococcus infection of the lungs, for example, non-hemolytic streptococci have been isolated from the peritoneal fluid. I have further demonstrated that streptococci found in the alimentary tract will invade the animal body following injections of dead or living colon bacilli as also after injecting various forms of streptococci. Numerous similar results have been recorded in the literature, but not uncommonly these have been misinterpreted.

It must not be forgotten that in injecting streptococci into animals we are overlooking some of the most important characters of these bacteria. Subcutaneous and intraperitoneal injections of large doses may serve as tests for the further invasive power of the bacteria from these sites, modified by the local injury resulting from the injections, while intravenous injection completely ignores the invasive character. The streptococci by this latter method, finding themselves in the circulation, naturally locate in various organs, and, according to the grade of virulence, will multiply in those tissues in which the susceptibility is of the corresponding grade. The irritation, both mechanical and that arising from the products of growth in the vehicle, will frequently bring about local reactions, which may or may not favor the development of virulence. Infiltration of the tissues with polymorphonuclear leukocytes will frequently follow large injections while only mononuclear response may result from small doses.

Streptococci derived from sources in which the natural infection did not result in a polymorphonuclear reaction may give rise, when injected in large doses, to such a reaction. It is therefore not to be concluded from the unnatural conditions of such experiments that the response elicited is fundamentally characteristic of the bacteria. The study of natural infection demonstrates that the two main groups of streptococci call forth quite different responses, and animal experiments would be of value if we could determine the minimal dose which calls forth any reaction, as this would more nearly approach the natural condition. The products

of growth of the bacteria, be they toxins or other excretions, probably determine the character of the response in susceptible tissues, and these two groups differ in the type of reaction they stimulate, the hemolytic streptococci calling forth more active responses and the non-hemolytic a slower and more chronic type of reaction. If we use the same dose of one streptococcus with a certain virulence and find the same tissues affected in the majority of the injected animals it will serve as a test to indicate the susceptibility of these tissues in the particular group of animals. Even varying doses may at times demonstrate the same thing. Further, this same streptococcus having had its virulence raised will attack other tissues which were resistant in the previous experiments. All these and many other points serve to emphasize the importance of the relations existing between the host and the infecting organism.

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An Analysis of the Vaginal Flora in Late Pregnancy

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AN ANALYSIS OF THE VAGINAL FLORA IN LATE PREGNANCY.

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THE importance of bacterial infection in the complications of pregnancy and the puerperium has led to many studies of the vaginal flora from almost as many and widely varied angles. Special organisms of particular pathogenicity have been exhaustively investigated, in addition to numerous researches of a more general character. Much labor has been expended upon the determination of the bactericidal effect, reaction, chemical character and other qualities of the vaginal secretion itself. And with all this, the question of the nature and mode of infection remains, at least in some degree, a vexed one. The streptococci, perhaps more than any other single group, because of their well-known importance in puerperal fever, have interested many; but as the investigations of this subject have not been entirely satisfactory, a routine study of vaginal cultures during the later weeks of pregnancy was undertaken, not to isolate only streptococci but rather to determine the characteristic flora of the vagina at a particular period by the methods at our command in a laboratory for routine clinical bacteriology.

The work was done during 1915–16 while the writer was resident pathologist at the Elizabeth Steel Magee Hospital. The pregnant women of the obstetrical wards, as well as those visiting the outdoor clinic prior to admission were available. The 130 cases were not selected in any way. They included simply the ordinary run of patients, both before and after admission to the hospital. All were apparently healthy, though the amount and character of vaginal secretion varied somewhat. In none was there evidence of an inflammatory process.

A brief historical review of the study of vaginal bacteriology is of interest. Doederlein's monograph, published in 1892, was the first systematic attempt to work out the important question of the normal vaginal flora. In it, he described the large Gram positive, facultatively anaerobic bacillus which bears his name, and noted its frequent association with a type of blastomycetes which he believed

to be the saccharomyces albicans or thrush fungus. Next in order of frequency in his cultures was the staphylococcus albus. Gonner, in 1887, described many organisms in vaginal smears, mostly bacilli. He believed that the vaginal secretions contained no pathogenic bacteria. Bumm also supported this view, while Winter believed that they were present in a state of lowered virulence, or even were without virulent qualities. Doederlein, in 195 cases, found streptococci in only eight. In inoculation experiments, but five of these were demonstrated to be virulent. Krönig, in 1894, published a series of 200 bacteriological examinations, in which, aside from the gonococcus and the thrush fungus, he found no pathogenic microörganisms. He found no streptococci. On the other hand, Joeten, in 1912, reported 100 antepartum cultures, with streptococci in 67, and 14 of these were hemolytic. In these cases, evidence of pathogenicity was wanting. Max Stolz, in 1903, published a report of a small series of pregnant women in which bacteriological examinations had been made. He divided his cases according to Doederlein's classification of normal and abnormal vaginal secretions. He then preceded to show that practically the same number and types of bacteria could be cultivated from both groups. These bacteria he was satisfied to name as cocci, bacilli and streptococci, without entering further into their nature than to say that the streptococci were facultative anaerobes, and were pathogenic for white mice. Bergholm, in a series of 40 cases, noted the constant presence of bacterial forms in the vaginæ of pregnant women. These he was able to obtain in anaerobic cultures. He also found saccharomyces in 16 out of 40 cases, though these were never seen in direct smear. Krönig found oidium albicans in 22 out of 167 cases studied. Walton and Medalia, working on streptococci in the vagina, found them present in from 10 to 40 per cent. of pregnant women. They reported extensively on the hemolytic and nonhemolytic forms without, however, differentiating them further. Küster, writing on the bacteriology of the normal vagina, concluded that the bacteria of the vagina were almost entirely saprophytic and nonpathogenic and were at least facultative anaerobes. True pathogenes, he states, are only present when there is an abrasion or wound of some sort, in which they are able to carry on their parasitical existence. Such organisms are only able to continue in this region by resisting the antagonistic symbiosis of the saprophytic flora, the high degree of acidity present, the relative anaerobiosis, the phagocytic properties of leukocytes, and possibly the immune properties of the fluid portion of the normal vaginal secretion. These are problems which will not

be discussed in the present study. In addition, the pyogenic staphylococci, pneumococci, the colon bacillus, the gonococcus, the Klebs-Loeffler bacillus, diphtheroid bacilli, tubercle bacilli, smegma bacilli and various anaerobic saprophytes have been reported in vaginal cultures.

From the data enumerated, the remarkable absence of definite identification of the bacteria isolated is striking, and with this in mind, the present study was undertaken. Particular interest was felt in the streptococci, both hemolytic and nonhemolytic types. The importance of determining as completely as possible the biological characters of these organisms, including their reactions on various sugar media was fully realized, in view of the fact that the streptococcus pyogenes could thus be identified from other hemolytic forms. The nonhemolytic streptococci were also completely identified by their sugar reactions, and gave in some measure, a clue as to the source of these organisms. In working out the streptococci the classification of Holman was followed. The staphylococci and the Gram negative bacilli were also identified according to the accepted methods, and other organisms were worked out as far as routine methods would permit. The cultures were obtained from women between the twenty-fourth and fortieth week of pregnancy, according to obstetrical calculations. A few were earlier, even before the diagnosis of pregnancy was fully established, and several cases were past the estimated date of confinement. As stated above, all were apparently normal cases, without elevation of temperature or local inflammatory reaction in the vagina.

The material for culture was obtained before any procedure other than a thorough cleansing of the external genitalia. A sterile speculum was introduced and opened so as to expose the vaginal vault and posterior culdesac. Free access to the vaginal vault being thus obtained, a slender wooden applicator bearing on its tip a small cotton swab was removed from the stoppered test-tube in which it had been sterilized, and introduced directly into the highest portion of the vagina, where a sample of the secretion in the region about the cervix was obtained. After being replaced in its tube, the swab was immediately taken to the laboratory. The original cultures were planted as soon as possible after receiving the swab. The usual laboratory routine was followed in this regard. The swab was first shaken in dextrose serum broth and then in plain broth. These fluid cultures were incubated at 37.5° C. for eighteen to twenty-four hours. Direct smears for staining were made from the same swab; but in any instance in which the presence of gonococci was suspected,

a separate swab was sent for smear preparations. The smears were stained routinely by Gram's method. Following incubation, the fluid cultures were examined by inspection and smear for evidences of growth, and if in the least suggestive, they were plated on human blood agar, using the streak method. These plates were incubated for a similar interval, and again inspected. The various types of colonies were identified by their gross appearance and by stained smears. Discrete colonies of the type or types present were then transferred to media suitable for isolation in pure culture, prior to complete identification.

In the identifying streptococci, the original character of hemolysis or nonhemolysis was again tested by transfer to a blood agar slant. After twenty-four hours' growth to develop this quantity, transplants were made to a set of four sugar serum broths, including lactose, mannit, salicin and inulin. These were incubated and observed daily for at least a week, during which time a record of rate of growth, acid formation and capsule development was kept. This method also identifies the pneumococci.

The Gram negative bacilli were differentiated by the ordinary media used in distinguishing the members of the typhi-coli group. This included four plain sugar broths, dextrose, lactose, saccharose and mannit (all containing Andrade's indicator and put up in Durham's tubes), agar, litmus, milk, Dunham's peptone solution for indol formation, and gelatin. Motility and the presence of capsules were routinely studied. Besides identifying the members of the typhi-coli group, this method of study made it possible to distinguish several Gram negative saprophytic bacilli.

Staphylococci were grown on plain agar as the best medium for obtaining a characteristic growth, with the development of color after several days. After twenty-four hours' growth on agar, transfers were made as stab cultures in deep gelatin, which were observed daily for liquefaction.

The findings in direct smear may be tabulated as follows:

No definite organisms (although all but one of these produced growth in cultures)	13
Gram positive cocci alone	11
Granular fusiform bacilli and short Gram positive bacilli	1
Gram positive bacilli and Gram positive diplococci	9
Diphtheroid bacilli and Gram positive coccoid forms	2
Gram positive diphtheroid bacilli alone	19
Barred, granular, fusiform Gram positive bacilli alone	1
Small Gram positive bacilli, often in diploforms	6
Gram positive bacilli, not further described	1

Gram positive bacilli, of fair size with square ends	17
Gram negative bacilli, large Gram positive bacilli and diphtheroid bacilli	2
Gram negative bacilli, large Gram positive bacilli and Gram positive diplococci	1
Gram negative bacilli and large square ended Gram positive bacilli	2
Gram negative bacilli and Gram positive coccoid forms	12
Gram negative bacilli alone	31

It will be seen that these findings covered a fairly wide range of organisms and that the cultural findings, which appear below, are at considerable variance with the direct smears. Absence of organisms in direct smear was reported in thirteen instances; but in all but one of these, one or more types were obtained culturally. Where only Gram positive coccoid forms were seen in smear, there was no constancy in finding cocci culturally. The same is true of the other types of organisms seen in apparently pure culture in direct smear. Cultures frequently gave evidence of other organisms in addition to those seen in smear, and as often an entirely different type. In cases showing several forms in direct smear, the final results were even more widely variable. The prominence of various Gram positive bacilli in direct smear, notably those described as "diphtheroid" and the large form with square ends is in sharp contrast to the cultural findings. The growth of these forms was almost uniformly unsuccessful although Loeffler's blood serum was used in addition to the other media in original cultures when diphtheroid forms appeared in the direct smears, and various anaerobic methods were employed in an attempt to recover the large Gram positive bacillary forms. One diphtheroid form was obtained in a pure, but feeble growth and its exact nature was not determined. None of the large square-ended bacilli were ever grown. The anaerobic methods included (1) a variety of media cultivated in anaerobic jars, (2) deep agar with and without a covering layer of sterile albolene and (3) litmus milk overlaid with albolene. Here it is to be noted that Krönig and Menge were able to grow the bacillus of Doederlein only on acid media, where it grew apparently equally well both with and without strict anaerobic conditions. Bergholm, however, did in one instance succeed in obtaining a culture of what he believed to be this organism on an alkaline medium. The preference of this organism for acid is likewise demonstrated by Krönig's results in studying the vaginal bacteriology of pregnant and nonpregnant women. He found that in 55 per cent. of vaginal cultures in pregnant women he was able to obtain B. Doederleini, while only 13

per cent. of similar cultures in nonpregnant women yielded this organism. This finding may be attributed to the greater acidity of the vaginal secretion in pregnancy. These points possibly indicate why the large, rather square-ended Gram positive organisms so frequently seen in smears were not obtained in culture, since the media used was neutral in reaction to litmus.

The results in cultures showed, in the 130 cases, no growth in twelve instances. Of these twelve, all but one had shown various bacteria in direct smear. In these smears, various Gram positive bacilli, mainly the large square-ended form, were found in nine instances. Beside the one showing both no organisms in smears and no growth, one showed Gram positive diplococci, and one Gram negative bacilli. From the remaining 118 cases, Gram positive cocci, including many varieties were grown 127 times. Gram negative cocci were found but once. Gram positive bacilli were grown nine times, and Gram negative bacilli seventeen times. Blastomycetes were grown nine times, an anaerobic streptothrix once and a member of the nocardia group once.

After this general survey of the cultural results, the findings are next indicated in greater detail. The cocci constituted the largest group, and may be subdivided as in the following brief tables.

Staphylococci.	
Staphylococcus albus (air form)	2
Staphylococcus pyogenes albus	85
Staphylococcus pyogenes aureus	9
Hemolytic streptococci.	
Streptococcus pyogenes	3
Streptococcus hemolyticus infrequens	1
An unidentified hemolytic streptococcus	1
Nonhemolytic streptococci.	
Streptococcus salivarius	5
Streptococcus fecalis	3
Streptococcus mitis	7
Streptococcus equinus	1
Streptococcus ignavus	2
Streptococcus nonhemolyticus	1
An unidentified nonhemolytic streptococcus	1
Pneumococci	4

And in addition the diagnosis "streptococcus only" was made in two instances, in which the organism was found in original cultures but died out before it could be isolated.

The Gram negative cocci included only one micrococcus resembling micrococcus catarrhalis. This organism did not grow satisfactorily, and could not be completely identified. The absence of gonococci in the series of cases studied is remarkable. In no instance was a direct smear suggestive enough to warrant an attempt at obtaining the organisms culturally.

Among the bacilli, the various members of the typhi-coli group were found much less frequently than might reasonably be expected. B. coli communis was found in ten instances, B. coli communior in three, while B. lactis aerogenes was isolated but once. In addition to the above Gram negative bacilli, one instance of B. proteus and two of saprophytic chromogenic bacilli remain to be mentioned. The Gram positive forms included one diphtheroid bacillus and five instances of B. xerosis. Although blood serum was inoculated from the original swab whenever diphtheroid organisms were seen in direct smear, no true B. diphtheriæ was grown.

Of the spore-bearing Gram positive bacilli only one member was isolated, identified as B. mesentericus. Finally, one chromogenic saprophytic Gram positive bacillus, and one poorly growing Gram positive anaerobic bacillus complete the list.

The marked difference between the findings culturally and in direct smear of bacilli broadly classed as Gram positive is interesting. Whether or not the organism last mentioned is to be considered an example of Doederlein's bacillus, one is unable to say, as it grew feebly and did not persist in cultures long enough to give an opportunity for study. The cultural and biological characteristics of the so-called Doederlein's bacillus are described as follows by Migula: "A medium-sized bacillus, rather slender; grows in 1 per cent. glucose broth. When transferred to glycerin agar it produces dewy, drop-like colonies. It is a facultative anaerobe." The description does not specify that an acid medium is essential, though this has been definitely stated by various workers, who have also noted that better results are obtained by employing a considerable amount of the secretion in the cultures. Our cultures were not made on acid media and only a relatively small amount of secretion was used. The consensus of opinion, too, is that of all the vaginal organisms this is the most saprophytic. Hence, less interest was felt in its cultural differentiation. The others, particularly the streptococci were of greater importance and interest. If the large Gram positive bacilli often seen in direct smears were this organism, it is not so remarkable that they were not obtained culturally, in view of the fact that media having a reaction suitable

for this organism was not employed, and only a small quantity of secretion was used in making the original cultures.

Blastomycetes were isolated in nine cases. These organisms were typical yeast forms staining strongly Gram positive. They gave somewhat different reactions on plain sugar broths in Durham's tubes, such as are used for the typhi-coli group. Of the nine strains isolated, one fermented only dextrose, forming acid and no gas; five fermented dextrose, with the formation of acid and gas; and three fermented both dextrose and saccharose, with the formation of acid and gas. All forms produced their reactions slowly and neither acid nor gas were produced in very great amounts. The organisms were not grown on special media for spore formation. The single instance of streptothrix was isolated in pure culture from a case which had shown long, Gram positive, granular bacillary forms, square ended and sometimes in pairs in direct smear. The nature of the organism was not further determined.

One member of the nocardia group was also isolated in pure culture, but its exact identification was not completed. The direct smear in this case showed Gram positive bacilli, Gram positive diplococci and Gram negative bacilli. In the culture a staphylococcus albus was also obtained.

The foregoing findings indicate that the vaginal flora is extremely variable. The types of organisms most resistant to acid among the ordinary pathogens are the streptococci and the typhi-coli group. Küster comments on the predominance of "acidophile" organisms in the vagina. Both of these groups produce acid in their growth on media, and in the case of the streptococci, Broadhurst has been able to recover viable organisms from media which showed an acidity as high as 5.3 per cent. The blastomycetes are also capable of flourishing in an acid medium. Hence, it is noteworthy that, after the staphylococci, large numbers of which were cultivated, as would be expected from moist skin or mucous surfaces, the next three in order of frequency were the streptococci(26), the colon bacilli(14) and the blastomycetes(9). Doederlein gave the acidity of the vaginal secretions as 0.4 per cent. lactic acid, and believed it to be somewhat increased in pregnancy, while recently Harada has shown that in pregnancy this reaches 0.9 per cent., and that the bactericidal effect is definite. The determination of the carbohydrate reactions of the streptococci was felt to be particularly important in view of the dearth of any definite information on this point in the literature. Walton and Medalia, in their extensive research on streptococci in the vagina, both ante- and postpartum, were content to classify

them as hemolytic and nonhemolytic, discarding the carbohydrate reactions as valueless apparently without having tried them out. They also stated that the determination of virulence by animal inoculation is of no avail, because of the great variability of factors concerned. Henrici, on the other hand, believes that carbohydrate reactions do not necessarily indicate virulence, basing his views on a long series of streptococci studied by their reactions on the carbohydrates and paralleled by the results of animal inoculations. Doederlein and Winternitz refer to the streptococci simply as "streptococci," without any further differentiation. Stolz, also, classified these organisms merely as streptococci. Schottmüller mentions an anaerobic streptococcus which he calls the "streptococcus putridus," and also speaks of the streptococcus of erysipelas. Seligmann divided the streptococci as hemolytic and nonhemolytic. He found the percentage of hemolytic streptococci low, and stated that the finding of streptococci seemed to have no prognostic value as to the progress of the case postpartum. Joeten likewise used only the presence or absence of hemolysis to differentiate streptococci, finding hemolysis no criterion of virulence. He believed that the presence of streptococci in the vaginal secretions was without prognostic value. Vareldo, working on cervicitis and endocervicitis, found streptococci which he was able to grow both aerobically and aerobically and on both acid and alkaline media. These showed pathogenicity for white mice, and differed in no way from "streptococcus pyogenes." Koblanck recovered many streptococci from vaginal cultures, but was quite unable to differentiate between streptococcus pyogenes and the less pathogenic forms. Natvig, too, comes to the same conclusion. He was able to differentiate the streptococcus pyogenes from an organism he terms the anaerobic streptococcus of Krönig. Being unable to go further, he was led to classify the remaining streptococci as atypical pneumococci, or "parapneumococci." Confusion with green streptococci doubtless was the cause of this error.

In the 130 cases studied, streptococci were never seen as such in direct smear, and only twenty-six strains were recovered culturally. Only three of these gave the carbohydrate reactions of streptococcus pyogenes, and as animal inoculations were not carried out, the virulence of these strains is not known. While the carbohydrate reactions may not be strictly indicative of virulence, they are undoubtedly of value for classification.

The routine conduct of obstetrics at Magee Hospital permits as

few vaginal examinations as possible, particularly in late pregnancy. In none of the cases studied was there any serious complication following delivery. Slight rises of temperature were noted, but in these cases blood cultures invariably proved negative.

Conclusions.—A study of the vaginal flora in pregnancy carried out according to the ordinary modern routine laboratory methods, reveals a variety of organisms, and various definite strains of each and is of particular interest in regard to the types of the streptococci and the organisms of the typhi-coli group.

A relation apparently exists between the ability of various groups of organisms to flourish in an acid medium, and the presence of these organisms, notably the streptococci, the members of the typhi-coli group, and the blastomycetes, in the vagina.

The presence in the vagina of streptococci giving the carbohydrate reactions of virulent organisms, as well as those of less virulent character but corresponding to forms recognized as having definitely invasive qualities, is comparable to that recognized in the other cavities, in which virulent or apparently virulent organisms are constantly present without giving rise to disease processes.

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CHLOROMA: WITH REPORT OF A CASE

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CHLOROMA: WITH REPORT OF A CASE*

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In recent years, there has been extensive literature presented upon the group of diseases associated with the blood-forming organs. This has, undoubtedly, been stimulated by the confusion of classification and insufficient knowledge of their etiological factors. Considerable evidence has been accumulated to show that many of the specially named blood diseases are closely related to each other, even to such an extent that some observers believe that they are transmutable. Cases closely simulating the one recently reported by Warfield and Kristjansen which showed the transition of lymphosarcoma to acute lymphatic leukemia and thence to Hodgkin's disease lend much to this latter view.

Chloroma is very closely related to the acute leukemias and probably should be considered under them. The term chloroma was first used by King in 1853, when he applied it to a case of greenish tumors of the head, coming under his observation four years previously. The first report of this condition is attributed to Allan Burns, who described it in 1823. He, however, did not attempt to name the condition. His case was one of greenish yellow tumor masses occurring about the bones of the head. Dock reported the seventeenth case to which reference is found in the literature in 1893 and briefly reviewed the sixteen previous cases. Since then, sixty-nine cases, classified as chloromata, have been reported.

From the cases which have been described it would seem that the term is not entirely appropriate if the condition is to be regarded as a separate pathological entity, inasmuch as cases have occurred in which all of the clinical and pathological features ascribed to chloroma have been present except for the green color, and others where only some of the nodules, glands or blood clots showed the green color at autopsy. "Nonchloromatous leukemia" has at times been applied to the former type of cases, but it also would appear to be a misnomer. Sternberg, in his classification of the diseases of the hematopoietic organs, describes under hyperplasia of lymphoid tissues with leukemic blood and having tumors originating in various situations and invading tissues, leukosarcoma. If the tumor masses of such a condition are of green color, the name chloroleukosarcoma is applied. Likewise such a condition with leukemia of myelogenous origin is named chloromyelosarcoma. These terms seem appropriate if they are used to describe a form of acute leukemia with an origin in the bone marrow, in which the cells are so malignant in type as to erode the bones to form tumor masses upon their surfaces, some or all of these masses presenting a greenish color. In most of the cases described as chloroma previous to that of Klein and Steinhaus, reported in 1904, the cell type was thought to be of lymphocytic origin and the condition was classified by various writers as a form of lymphatic leukemia, lymphosarcoma or a transitional stage between them. Since then, however, the majority of authors have classified the cell as of myelogenous origin and the condition as a form of acute myelogenous

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leukemia. Both Treadgold and Burgess convey the idea that it is probably always of myelogenous origin. The increase in the proportion of reported cases of myelogenous origin is probably due, as suggested by Burgess, to the more thorough examination of the cells both morphologically and biologically, as by the oxydase reaction, which he thinks has shown that certain of the cases formerly classed as acute lymphatic leukemia must be considered as myelogenous. Forman and Warren recently reported a case of myeloma, many of the cells of which, by ordinary staining methods, seemed to be plasma cells. The cells, however, contained oxydase granules, showing them to be of the myelogenous series. Without such examination this case probably would have been called plasmoma.

That the condition is always due to a primary involvement of the bone marrow is shown by the fact that in practically all cases in which the bone marrow was examined it was found altered; that the location of the tumor masses attached to the bones is always found in the short bones and those of the skull, in the marrow of which the hematopoietic function is still active; that the cells evidently have grown directly through the bones to form the masses, as the surfaces of the bones are eroded and the masses fairly well attached; and that the cells in a number of cases have been definitely proved to be myeloblasts and myelocytes since their protoplasm either showed granules by differential staining methods or oxydase granules upon application of the oxydase reaction.

The blood picture of an acute leukemia, concomitant with chloroma shows the same type of cell which is predominant in the green tumor, as well as in sections of the bone marrow. Burgess states that the highest leucocyte count was 1,880,000 per cubic mm. In a few cases no increase of white blood cells was noted and for these forms the term "aleukemic chloroma" or "chloromatous pseudoleukemia" was suggested. However, there is not sufficient evidence to introduce this terminology as indicating a distinct type of disease.

Although the terminology is confusing, it would seem that when the term chloroma is used, a type of leukemia is referred to in which there is the formation of green masses of immature white blood cells. The leukemia is probably always myelogenous in character and is due to a primary hyperplasia of the red bone marrow. The marrow cells develop to such a degree that they erode and grow through the bone to form green tumor masses upon its surface, as well as evidence metastatic power to enter the blood stream and lodge in distant organs, where they may multiply. Some or all of the cell collections, whether seen as tumors upon the surfaces of certain bones, as nodules in the organs, or occurring in the blood clots, bone marrow or glands, may show the greenish color at autopsy. Treadgold says, "Since it is usual in chloroma for a varying proportion of the lesions to show no green color, it is theoretically possible to get a fairly acute type of myeloblastic leukemia, bearing a general resemblance to chloroma, but without the green lesions."

The clinical and pathological features of most of the cases are similar. It occurs more frequently in children, particularly males. When not occurring in children, the most frequent age incidence is after the fourth decade. The patient generally complains of weakness, anemia, pain due to pressure of tumorous masses, and a tendency to hemorrhage. Exophthalmos is frequent, due to

green tumor formation in the orbital fossæ. The disease runs an acute course from weeks to months and so far as known is invariably fatal. Leukemia is present. At necropsy, the chief findings are flattened greenish tumors over the inner surface of the bones of the head, vertebræ, sternum, or ribs. The bony surface beneath is eroded and to it the tumor is attached. The marrow spaces are increased in size and the bony trabeculæ rarefied. Tumor nodules may be found in the various organs and some of the blood clots may have the greenish color. An absolute diagnosis cannot be made, except by encountering the green color in the tissues. This has been done in several cases during life by finding the presence of green nodules subcutaneously. Attempts to diagnose by the symptoms and location of masses is only conjecture as the same may occur in acute leukemia, lymphosarcoma and myeloma. The diagnosis was made in a case reported by Butler upon the following points; age 11 years, acute leukemia, exophthalmos and right-sided deafness. The exophthalmos in this case, contrary to expectation, was found not due to the size of the orbital tumor mass but to vascular engorgement. This shows how easy it is for one to err in the diagnosis of certain manifestations.

While the report of the two cases by Gould and Le Wald is noteworthy, yet in the absence of autopsies and definite leukemia, their classification as chloroma is uncertain. Their diagnosis before death was made upon age (children), exophthalmos, periosteal and medullary changes of the bones, glandular enlargement, and microscopical picture of glands removed from the neck. No leukemia was present in the first case and the white blood count in the second case was only 16,500. Such a count could be present in lymphosarcoma or many infections.

The following case was under the service of Dr. J. A. Lichty to whom I am indebted for the clinical notes:

The patient, an adult male, age 36 years, was admitted to the Mercy Hospital, November 16, 1915. He complained of weakness and pain in the right chest and beneath the sternum. His family history was negative. There was previous history of measles, mumps, whooping cough, diphtheria, typhoid fever, malaria, lues and Neisser infection. His luetic infection had occurred seven years previously and for one year he had received mercury by mouth and inunctions. Cardiorespiratory and digestive systems were negative. On admission, physical examination showed a well developed male, not acutely ill. A moderate amount of anemia was present. The pupils were equal, regular in outline, symmetrical and reacted to light and accommodation. No exophthalmos or other ocular signs. Some purulent exudate was present over the left tonsil. Very little glandular enlargement present. The thorax showed a distinct depression over the right apex and subclavicular region and very little rotation of ribs of the right side on respiration. The percussion note over the right apex, right subclavicular region, and region lateral and inferior to the right scapula was impaired. No ascites. The liver was palpable at the costal margin. The spleen seemed enlarged to percussion but not palpable. Wassermann reaction for lues was negative.

HEMATOLOGICAL EXAMINATION.

	Nov. 17, 1915.	Nov. 20, 1915.	Nov. 22, 1915.	Nov. 26, 1915.	Nov. 30, 1915.	Dec. 7, 1915.
Hemoglobin	30			20	15	
Red blood cells	1,632,000			872,000	600,000	675,000
White blood cells	53,000	44,000	43,000	45,200	138,200	320,000
Myeloblasts	73	76		82	77	
Polymorphonuclears	9	11		11	7	
Transitionals	1				2	
Large lymphocytes	11	6		2	3	
Small lymphocytes	6	7		5	11	

Blood Smears.—The blood smears were stained by Wright's method. The white blood cells were greatly increased in relative proportion to the red blood cells. A number of nucleated reds were observed. The leucocytes varied in size from 8 to 21 μ in diameter. All of these cells, even the forms appearing as small lymphocytes, were pale staining. Sometimes the nuclei of the small lymphocytes showed vacuolation, often giving a rosette arrangement. The large mononuclear forms classified as myeloblasts were round or oval and had very pale, large, single nuclei, which occupied the greater portion of the cell so that only a relatively small rim of cytoplasm appeared at the periphery. The nuclei did not appear reticulated. The cytoplasm was faintly basophilic and slightly darker in staining quality than the nuclei. At the time when these smears were made there was no mention of specific granules in these cells. It is probable, however, that they were somewhat different from true myeloblasts, as a new examination of the smears one year later showed the presence of a small percentage of both eosinophilic and basophilic myelocytes. The granules of the polymorphonuclear leucocytes were very faint and could not be made out with the stain (Wright's) used. Possibly with better staining methods for granules these could have been demonstrated in some of the cells termed myeloblasts. Polymorphonuclear leucocytes were few in number. During life no examination was made for oxydase granules in the cells of fresh blood films. This was attempted some time after death, but the films were too old to demonstrate the reaction.

The clinical diagnosis was "myeloblastic leukemia." The patient died three weeks after admission to the hospital. During this time the white blood count as shown above increased gradually from 53,000 to 320,000 cells per cubic mm. An autopsy was performed 4 hours after death by Drs. W. W. G. Maclachlan and J. W. Fredette.

AUTOPSY.

The body was that of an adult male measuring 160 cm. in length. The body was fairly well developed, but poorly nourished. The skin surfaces were very pale. There was no rigor mortis and only slight lividity on the dependent parts. The pupils were equal and moderate in size. Scattered over both arms, upper left thorax and abdomen, were a number of tiny petechial hemorrhages. The thorax was well formed. The abdomen was slightly flattened. There were no scars on the penis. The anus was normal. There was slight edema of the ankles.

Thorax.—On both sides there were some fibrous adhesions over the posterior surface of the lungs and also at the apices. About 100 c.c. of clear straw-colored fluid was present in each pleural sac. The pericardial sac contained a clear straw-colored fluid in a quantity of about 100 c.c. In the fat over the pericardium were a number of petechial hemorrhages. An occasional hemorrhage was also noted on the parietal and visceral pericardium. Lying opposite the left apex of the lung beneath the parietal pleura and over the inner surface of the ribs and also on the bodies of the thoracic vertebræ there was a thick, quite green, firm, smooth tissue, forming a layer, which, although well attached to the bony structures underneath, could be peeled away leaving evidences of an eroded underlying bone. This tissue when removed measured 5x4x1.3 cm. Its pleural surface adjacent to the lung showed carbon pigmentation to a very marked degree, otherwise it was green. On section, the cut surface had a glassy, smooth appearance. There were some fibrous tags running between this tissue and the apex of the lung. The green color faded gradually after the removal of the tissue. The pleura covering the ribs showed many tiny petechial hemorrhages.

Left Lung.—Weight 630 gm. The posterior surface and the apex of the upper lobe showed a few dense fibrous adhesions. The lung was quite black in color showing much anthracosis. It felt moderately firm but crepitated in most places. Section through the lower lobe showed a cut surface, fairly dry, of grayish pink color, and with very prominent nodules of anthracotic pigment. The upper lobe was a little lighter in color and somewhat moister. At the apex, opposite the fibrous adhesions, was a small area of fibrosis in the lung substance. There was no calcification nor caseation noted here. The bronchi were free. The peribronchial glands showed marked anthracosis, but no evidence of tuberculosis.

Right Lung.—Weight 800 gm. There were some fibrous adhesions over the posterior portion of the lower lobe and on the diaphragmatic surface. The lung felt firm but crepitated in most places. The lower lobe, on section, showed a somewhat moist pinkish gray surface, glassy throughout, with numerous nodular areas of anthracosis. Petechial hemorrhages were also seen in the lung substance. There was no consolidation. The upper lobe showed the same characters, and fluid could be expressed from its substance.

The edema in this lobe was more marked than in the other lobes or in the other lung. The bronchi showed much frothy fluid but their lining was not congested.

Heart.—Weight 415 gm. The heart contained a large quantity of soft chicken fat clot of a more gray color than that usually seen. This clot was present in all chambers of the heart. The heart valves had very little noticeable change. The mitral valve showed a slight amount of fibrous thickening. Scattered over the surface of the heart were petechial hemorrhages. Shining through the pericardium, over the ventricles, one could distinctly discern yellow fatty stippling in the heart muscle. When the heart was opened this stippling was beautifully seen shining through the endocardium, particularly in the papillary muscles and columnæ carnæ. The myocardium was pale yellow in color. On section through the myocardium of the left ventricle the diffuse yellow stippling was well brought out. The muscle was of fair consistency. The F. O. was closed. There was no evidence of fatty change in the endocardium, but petechial hemorrhages were particularly noticeable under and in the endocardium of the auricles. The coronary arteries showed patent lumina with no diminution in size or change in the lining. The aorta was thin and elastic, and showed but little yellow intimal change.

Abdomen.—The fatty layer was well marked and of a pale yellow color. The recti muscles were bright red and quite thick. The great omentum was fatty and covered the upper coils of the small intestine. The intestines were somewhat collapsed. There was no fluid in the abdominal cavity. The appendix was small showing a slight constriction about the middle due to a band of fibrous adhesions. The organ lay behind the lower end of the cecum and pointed upwards. The mesenteric glands were not enlarged. Some were slightly reddened, suggestive of the hemolymph gland type. Throughout the mesentery were many tiny petechial hemorrhages. The liver reached to the costal margin. The diaphragm arched to the right 5th rib and 5th space on the left.

Stomach.—The stomach was of good size. There was a pale smooth healthy looking lining. The pylorus was small and normal.

Intestines.—The small intestine showed nothing of note and was healthy. The lymphoid follicles were not enlarged. There was a good deal of sacculation of the wall of the large bowel, but no diverticula were noted.

Liver.—Weight 1825 gm. Measured 29x17x9 cm. The margin was sharp. The surface was smooth and shiny. Through it yellowish stippling could be seen. On section the liver was of a chocolate color, swollen and glassy. The outlines of the lobules were not distinct. Scattered thickly over the cut surface of the liver was a fine pinhead sized, yellowish white stippling. These areas were not regular in size. They appeared to lie in the outer portion of the lobule. The whole cut surface was somewhat nutmeg in appearance, although no central zone of congestion in the liver lobule was present. The liver surface was more brownish than the typical nutmeg type. In consistency the liver was about normal. The gall bladder was small and contained about 50 c.c. of tarry bile. The wall was thin and pigmented by bile on its inner surface.

Pancreas.—Measured 19x3x2 cm. The organ was firm. The cut surface showed grayish lobules which were normal.

Spleen.—Weight 190 gm. Measured 13x8.5x3.5 cm. The notches were quite distinct and the capsule appeared a little wrinkled and was covered by a geographical mottling of white lines suggesting lymphatic vessels. On section through the spleen, the organ appeared fairly firm, and little substance could be scraped off with the knife. The cut surface showed very prominent Malpighian tufts. The trabeculæ were but little evident. At two points a slightly darker spleen substance was observed. These areas were roughly triangular, but not clearly outlined. They were not suggestive of true infarction. In size these two areas were 1 cm. across the base and 1.5 cm. in depth.

Left Kidney.—Weight 235 gm. Measured 12x7x5 cm. The capsule peeled readily leaving a slightly granular and extremely pale cortex. In the capsule there were a few petechial hemorrhages. On the cortex there was a stippling of congested vessels. Scattered over the surface of the cortex were a number (about 12) of round slightly raised bodies 2 mm. in diameter. On section through these bodies they were seen to extend into the cortex about 2 mm. They had a light green color, were perfectly smooth, clearly outlined, and of the consistency of the cortex of the kidney. On section through the kidney the cut surface presented marked pallor, decided swelling of the cortex, and an indefinite marking. The glomeruli were poorly shown. In the deep cortex several green nodules similar to those described on the surface were to be seen. There was also some diffuse, whitish streaking and stippling which gave the cortex a rather granular appearance. The

fine capillaries of the cortex stood out prominently. About the pelvis there was considerable fat. The pelvis and ureters were healthy.

Right Kidney.—Weight 200 gm. Measured 5x5x3 cm. The capsule peeled fairly readily leaving very pale cortex with fine stippling of congested vessels on the surface. Similar small slightly green oval bodies were noted on the cortex. The cut surface of the kidney showed the same appearance as the left, with pale, swollen cortex and indistinct marking. There was one more decided green nodule in the cortex of the same size as the others. The deep cortex was similarly thickened, showing yellowish streaking and stippling as seen on the opposite side. The pelvis and ureters appeared free. There was a moderate amount of fat about the pelvis.

Adrenals.—The adrenals were of good size and showed marked yellow cortical layers and small white medullary portions.

Bladder.—The bladder was of good size. The wall was smooth and pale. The ureters were patent. The prostate was small and pale in color. The cut surface was glassy.

Testicles.—The testicles were of normal size. The cut surface showed a brown, soft character. The tubules could be easily pulled out.

Bone Marrow.—The bone marrow of the femur was pale red in color and appeared very moist. The color was darker and more intense than the normal marrow. In the marrow a large amount of cancellous bone tissue was found.

MICROSCOPICAL EXAMINATION.

Green Tumor Mass in Pleura.—The section showed a very cellular structure. The stroma was loose and appeared in most places as a fine reticulum. In other places it was denser and showed numerous collagen fibers. The only blood vessels seen in this stroma were capillaries. The predominant cell was rather large, about 12 micra in diameter, and mononuclear. The shape was round or slightly oval. The cytoplasm (stained with eosin and methylene blue) was neutrophilic and contained no specific granules. However, with higher magnification the cytoplasm was seen to have a ground glass appearance. A cell membrane was present. This cell had a large round, oval or sometimes irregular nucleus, vesicular in character, with a definite nuclear membrane and rather scattered, coarse, deeply staining chromatin granules or masses. Exclusive of these scattered chromatin masses, the nucleus was pale. Cells with smaller deeply staining nuclei and a relatively great abundance of neutrophilic cytoplasm were rather common. There was also present a number of polymorphonuclear leucocytes and eosinophilic and basophilic myelocytes. Very few typical lymphocytes were seen. Clear nuclear division was not seen, but binucleated forms were present. One of the sections showed the tumor cells to have entirely surrounded several large nerves. Fat globules lay between the tumor cells in many places. Another section of the tumor showed the cells to have surrounded a spinal ganglion. Some of the cells had invaded the substance of the ganglion.

Bone Marrow.—Section of the bone marrow showed a moderate congestion and a slight amount of marrow fat. The bone marrow cells were nearly all of the types described in the section of the tumor. About one per cent of the cells were lymphocytes.

Lung.—The section showed a deposit of granular precipitate throughout the alveoli associated with considerable red cell infiltration. Some of the alveoli contained fibrin. The walls of the alveoli were thickened, due to the dilated blood capillaries filled with tumor cells lying in the alveoli and surrounded by masses of fibrin and red blood cells. A moderate number of polymorphonuclear leucocytes were also noted. There was considerable anthracotic pigment about the vessels and bronchi. One of the large pulmonary vessels contained thrombi, made up of tumor cells, blood and fibrin. Occasionally, endothelial cells containing anthracotic granules were seen lying behind the alveoli. The tumor cells seen in the blood vessels, when stained with hematoxylin and eosin, had much the appearance of plasma cells.

Heart.—The section showed a rather loose, somewhat edematous interstitial tissue, which caused a moderate separation of the muscle fibers. The fibers were not very clear in their staining. Their transverse striations were not well seen, though the longitudinal ones were much better brought out. The nuclei were clear. There was very little pigment about the nuclei. The muscle fibers further had a finely granular, vacuolated appearance. There was no cellular infiltration present, but in the capillaries an unusual number of cells were seen which were similar to those seen in the blood smears.

Liver.—Section of the liver showed some congestion. The general outline of the

liver lobules was a little altered by the presence of large areas of necrosis. These necroses lay mostly in the central zone, although many reached into the more peripheral parts of the lobule. In the necrotic areas, there was an infiltration of cells similar to the type of cells seen in the tumor. A few polymorphonuclear leucocytic cells were seen. An infiltration of the tumor cells was also seen around the portal systems. Under high magnification, the indistinct shells of the liver cells could be still made out. In other portions of the section, liver cells of the central zone appeared very watery, showing but a cell membrane and nucleus. The rest of the liver tissue, particularly the peripheral zone, was relatively healthy, although the cells were swollen and granular. Much bile pigment was present in the liver cells throughout. The sinusoids were dilated and filled with granular precipitate. The bile capillaries were also dilated. In the sinusoids were many tumor cell elements of the usual type. Lymphoid cells were also seen in moderate numbers about the portal systems. Fat vacuoles were numerous in the central zones of the lobules.

Spleen.—The section of the spleen showed no congestion. The follicles were clear in outline. The trabeculæ were not large or numerous. In some of the follicles, masses of hyaline were to be observed. The sinuses were packed with mononuclear cells, similar to those of the green tumor mass. Through the section much blood pigment was noted within the endothelial cells. A hyaline change was observed in the walls of many of the vessels. The pulp was filled with cells similar in type to those found in the blood stream elsewhere, and also to those noted in the tumor mass. The polymorphonuclear leucocytes were few in number. The stroma in the spleen was not increased. In one portion of another section of the spleen was seen a large area surrounded by fibrous tissue. In the center of this area, there was a homogeneous pale blue staining material. Surrounding the area of fibrosis, there was a rather thick wall of tumor cells.

Kidney.—The section of the kidney was taken through one of the green nodules. There was also a good deal of uninvolved kidney tissue present in the section. The tubules showed granular looking cells with a moderate amount of debris in the lumen. The cells were quite irregular in outline and some were devoid of nuclei. The glomeruli were not changed, except in their capillaries, where a few abnormal cells were seen. In the capillaries of the interstitial tissue, tumor cells were numerous. The green nodule was seen to be a mass of tumor cells, which, in the center, had entirely replaced the tubular structure, while towards the periphery the necrotic remains of tubules were still to be seen. Near the outer margin of the tumor mass, the tubules were separated, but still living. The outline of the tumor nodule was fairly regular and quite devoid of any capsule, while the kidney tissue adjacent appeared normal. The cells of the nodule were the same as those noted in the tumor elsewhere. Another section of the kidney showed a little connective tissue increase following the course of the blood vessels. An occasional glomerulus was fibrosed.

Sections of the pancreas, prostate and adrenal showed normal characters.

Postmortem Bacteriology.—Cultures of the heart blood showed streptococcus pyogenes.

Oxydase Reaction.—Examination for oxydase granules by the Schultz method was made with the tissues one year after death. No oxydase granules were seen by this method due to the age of the materials. However, with Graham's method, which will stain the granules after a long period of time has elapsed, the majority of the tumor cells gave a positive oxydase reaction.

Anatomical Diagnosis.—Chloroma; myeloblastic leukemia; hyperplasia of bone marrow; chloroma of ribs, vertebræ, pleura and kidney; fatty degeneration of heart and liver; old bilateral pleural adhesions; petechial hemorrhages of skin, pleura, pericardium, endocardium, heart, mesentery, and lung; fibrosis of lung (right apex); anthracosis of lung; central necrosis of liver; edema of liver; enlarged spleen (slight).

Resume of Case.—The patient was a man of 36 years, complaining of weakness and pain in the chest. He had no exophthalmos, or glandular enlargement. Repeated examination of the blood showed a progressive leukemia. Clinical diagnosis was myeloblastic leukemia. At autopsy there was found a greenish tumor mass attached to the inner surface of the ribs and bodies of the vertebræ which when peeled out left evidence of erosion of the underlying bone. Green nodules were found in the cortex of the kidney. The bone marrow of the femur was hyperplastic. Petechial hemorrhages were present in the skin over the arms, thorax, and abdomen, beneath the pericardium and endocardium, in the lung, mesentery, and kidney capsule. The predominant cells of the blood were similar to those of the bone marrow and of the green tumors. Oxydase granules were present in these predominant cells showing them to be of myelogenous origin.

The study of this case contributes nothing to the etiology of the condition. As with other tumors, nothing is known of the causative factor. The presence of streptococcus pyogenes in the heart blood at autopsy is indicative of a terminal infection coincident with the low bodily resistance present just before death and has no etiological bearing. Sternberg cites eleven cases of acute myeloblastic leukemia, nine of which showed organisms either in the spleen, heart blood, or bone marrow. Seven of these cases showed streptococci, six times alone and once combined with staphylococcus aureus; one showed staphylococcus aureus alone and one staphylococcus aureus with streptococcus and influenza bacilli. He concluded that leukemic blood could be obtained in various diseases and that many cases which had been diagnosed as leukemia were but the reactions of the blood-forming organs to the original infections, and that the above cases of "so-called acute myelogenous leukemia" were nothing other than acute general infections which proceeded with myelogenous and myeloid metaplasia and were to be differentiated from the true and genuine leukemias. He offered this in explanation why some of the so-called "acute leukemias" can be cured while the true leukemias always have a fatal ending. But when it is considered that Strauch, in a series of two thousand postmortem blood cultures found an organism in 50.1 per cent of the cases and Fredette in one hundred and nineteen blood cultures taken immediately after death found organisms in one-third of the cases, it is quite probable that some of Sternberg's infections were terminal ones and were not the cause of the leukemic blood pictures. Rother found the same blood picture in a case of acute miliary tuberculosis as in myelogenous leukemia, but there is no way by which we can exclude a myelogenous leukemia as being coexistent with the acute miliary tuberculosis. Gans also recognized a similarity sometimes existing between the blood picture caused by infectious diseases and the blood picture present in spontaneous disease of the myelogenous system.

Although the case under discussion occurred in an adult, the great majority of cases are seen in children. This is sometimes explained as due to the fact, that in childhood there exists a relatively greater amount of red marrow and the hematopoietic organs are more active. But why should not myelogenous leukemia also occur more often in children, if this is the cause? The cell in chloroma is often more embryonal than that found in the ordinary type of acute leukemia. This, and the fact that the cell appears more malignant than that of acute leukemia may have something to do with its occurrence in children.

Color of Chloroma.—The greenish color of the chloromatous mass over the ribs and vertebræ faded rapidly on exposure to light and air. Portions of this mass kept in formalin regained its greenish color upon the following day, when immersed in hydrogen peroxide solution. After a period of one year in formalin, the tissue did not regain its former color after a like treatment. The same occurred with regard to the color of the green nodules of the kidney. The green color did not go into solution in either the formalin or the Zenker's solutions in which tissue was preserved. Nearly all observers noted the rapid fading of the color on exposure to light and air, and that the color cannot be preserved by means of chemical solutions, nor can it be recovered by ordinary

aqueous solvents. Exceptions, however, are found to these usual findings. Dock and Warthin in their case (1904) noticed a temporary increase in the depth of color after the removal of the tissue. Alt found that the tissues in his case retained their dark green color in formol solution and the fluid itself was a dirty green color. Risel reported that the color was not preserved in Kaiserling's solution. Burgess observed that tissue preserved in 10 per cent formalin for three years regained its former color in hydrogen peroxide and that in one instance the color was preserved several weeks in a strong solution of sodium bicarbonate, and to a very slight degree in certain of the tissues fixed in formalin and in Kaiserling's solution. Potassium hydroxide restored the color slightly to formalin treated tissue. Walls and Goldsmith say that the color in their case persisted in Kaiserling's solution for four and one-half years. Ayers found that on placing the green tumor in alcohol, the color disappeared entirely within twenty-four hours, but a specimen kept within a corked bottle retained its greenish color. The bone marrow of the tibia in this case showed a redder marrow than is usually present. The character of the tissue of the ribs and vertebræ, where one would expect more change present, was not examined. Burgess thought the redness of the bone marrow in his case was due to congestion of the capillaries. About seven cases have been reported which showed green marrow in some of the bones.

Various theories have been offered for the green color. The variety of the color reactions reported has led some observers to the opinion that it is not always due to the same pigment. By some it has been attributed to iron or fatty substances, but neither of these has been demonstrated as the cause. Reynolds held that the greenish color was of the nature of a fatty acid combined with iron. Walls and Goldsmith concluded that the color was not due to a foreign pigment such as iron, and believed that the consensus of opinion indicates that it is something inherent in the cells of the tumor masses, much the same as the chlorophyl of green plants. Schmidt suggests that the color might be due to the shape of the cells. Risel, Lubarsch and Weinberger demonstrated that the color was not of bacterial origin. Treadgold found that the green color is not present from the beginning, but that it makes its first appearance in the early lesions, and, therefore, that cellular degeneration plays a part in the formation. This degeneration may be due to the age of growth or facilitated by the toxemia. He suggests that possibly a degeneration of the granules or the perigranular protoplasm of these cells, or an abortive attempt to form granules, is the real source of the color, aided by broken down products of hemoglobin.

Sections of the green mass were stained for hemosiderin by Nishimura's modification of the Perls reaction and for fat by Sudan III, but neither were found to be present in the chloroma cells. Risel demonstrated hemosiderin granules in the tumor cells, but did not ascribe the color to these. Lubarsch was unable to find pigment granules in either sections or fresh preparations. Dock (1893) noticed abundant highly refractile granules in the cells of frozen sections. Huber and Chiari found granules which they thought were fatty in nature. Von Recklinghausen believed the color to be of a parenchymatous nature similar to the color of old pus. In the case of Dock and Warthin (1904) no pigment granules were present. Osmic acid and Sudan III tests were nega-

tive. That the color is not a postmortem finding is proved by the green lesions noted during life. Dock suggested that "the peculiar color was simply an exaggeration of the greenish tint so common in the blood clots and neoplasms of leukemia."

At the suggestion of Dr. W. W. G. Maclachlan, examination was made of the white blood cells from a case of myelogenous leukemia at the Mercy Hospital. The leucocytic count was 1,000,000 per cubic mm. Over ninety-nine per cent of these cells showed oxydase granules. Blood was drawn into a test tube with sufficient sodium citrate solution to prevent clotting, and the test tube was corked and allowed to stand twenty-four hours. When examined the buffy coat of white blood cells had a yellow color with a faint greenish tint. After standing for five days in the ice box, this layer showed a decided greenish color and the serum also had a slight greenish tinge. Upon shaking the tube and mixing the red blood cells and the leucocytes, the greenish color was entirely obliterated by the red. The formation of this distinct greenish color in the leucocytes on standing five days, emphasizes Treadgold's theory that the color is not present from the beginning, but that cellular degeneration plays a part. If this greenish color has any relation to that of chloroma, one might expect it where myelocytes and myeloblasts are present *en masse,* as in the cellular tumors of chloroma, which has but little stroma and is practically devoid of red blood cells. Chloroma would then be a type of myelogenous leukemia where the myelogenous cells appeared in dense collections. However, the green color observed in the myelocytes of the blood did not fade on exposure, nor did it deepen on addition of oxidizing reagents. That these two greenish colors may have a relation seems possible, but evidently they are not identical. A similar examination was made of the blood from a case of lymphatic leukemia where ninety-five per cent of the cells were lymphocytes. No green color whatever developed in the layer of white blood cells in this case.

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Bronchiolitis Obliterans following the Inhalation of Acrid Fumes

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BRONCHIOLITIS OBLITERANS FOLLOWING THE INHALATION OF ACRID FUMES.

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The developmant of excessive quantities of fibrous tissue in the lung is a relatively frequent occurrence in adults. The majority of these fibroses, however, have no appreciable effect upon the function of this organ. At autopsy the presence of pleural thickening with subjacent pulmonary fibrosis receives but passing notice, and the sclerosis of the lymphatics, particularly as a consequence to moderate grades of anthracosis, are noted during the examinaton of the tissue. The development of connective tissue under these circumstances does not encroach to any extent upon the alveolar structures, and the compensatory activity of the remaining lung is sufficient to carry the new burden without evincing any clinical symptoms. Under these conditions the bronchioles are in no way affected. Fibroses are also common in the areas of healed tuberculosis. These are most frequently encountered in the apex of the lung when more or less puckering is produced. But here, again, the larger tracts of lung tissue remain uninvolved and the effect upon the respiratory function is usually negligible.

More important are the fibroses which diffusely or sporadically involve the parenchyma of the lung. In interstitial pneumonia somewhat large areas of the lung tissue show a thickening of the alveolar walls, often developing to such an extent that the air sacs are considerably narrowed. Under these conditions the fibrosis localizes about the vascular channels in the alveolar septa, and to some extent about the bronchioles. The latter may eventually suffer narrowing of their lumina through the contraction of the surrounding fibrous tissue. Portions of the lobes or even an entire lobe may be thus sclerosed and have but little value for respiration. The remaining portion of the lung tissues may adequately compensate the lack of function in this portion of the lung and the individual show no signs of the respiratory impediment.

Finally, there is another type of fibrosis which, although less frequent, has a clinical importance. This type has been referred to as fibrous pneumonia. The condition is met with in various forms, sometimes appearing as a lobar process representing an unresolved

organizing lobar pneumonia, at other times being found as a lobular process. It is particularly the latter group in which our interest at the present time is centered. This lobular pulmonary fibrosis shows the presence of connective-tissue plugs filling the air sacs in small clusters of alveoli. Outside the affected portion of the tissue the alveoli are relatively normal. Thus one finds scattered through the lung substance small areas of fibrosis which tend to obliterate groups of air sacs and appear as milia widely disseminated. Here, again, an analysis distinguishes types of this fibrous bronchopneumonia. Some of them, and they are the majority, arise as a sequel to an acute bronchopneumonia and simulates the fibrosing process observed in the organizing unresolved pneumonia. A smaller group, however, and of these there are only 6 cases on record, the condition appears to arise primarily within the bronchioles and a few neighboring alveoli. In them there is no evidence of a preceding acute bronchopneumonia with organization of its exudate, but the fibrosing process appears to arise spontaneously from the walls of the bronchi and alveoli. In some instances an irritant has been briefly present inducing an inflammatory reaction, but in others no such irritant can be demonstrated. The irritant has usually been of the nature of irritating gases to which the individual has been accidently subjected. The following case is one of this latter group:

Case History. J. C., male, aged thirty-nine years, a laborer in a chemical works, gave a history of good health until the present illness. He also gave a history of lues with secondary skin lesions (time not stated) as well as a gonorrheal infection three years ago. He has used tobacco considerably.

Present Illness. The patient dates his present illness to an explosion at the chemical works three weeks previous to admission to the hospital. In this explosion, when various chemicals were being mixed in the preparation of trinitrotoluene, he was subjected to the breathing of irritating gases. Other than the discomfort and cough at the time of the accident he was not seriously ill. A few days later, however, he suddenly became dyspneic, at first observed on slight exertion, but later being continuous and accompanied by much sputum. The symptoms became progressively worse, along with a feeling of drowsiness and the development of edema of the ankles.

Physical Examination. He was a slightly built man, assuming the upright posture in bed. He had great respiratory distress, a dry, hacking cough, marked cyanosis, and a general slight anasarca. His pupils were irregular and reacted poorly to light and accommodation. His oral hygiene was poor, the tongue being coated, and the teeth showing pyorrhea alveolaris. Marked carotid pulsations were observed in the neck.

The heart occupied a normal position and showed no change in size. A blowing murmur transmitted to the left axillary region

was heard at the apex. There was a slight diastolic murmur at the apex, also heard at the second right interspace and transmitted along the vessels of the neck.

The respirations were short and snappy. Tactile fremitus was increased over the left upper lobe anteriorly; over this area the percussion note was somewhat flat. Auscultation revealed moist crepitations over the greater portion of both lungs. Tubular breathing was present over the left upper lobe.

There was slight movable dulness in the flanks of the abdomen and the extremities showed edema about the ankles and hands. There was a small amount of albumin in the urine, with an occasional hyaline and granular cast. The temperature reached its highest at 101.8° F. The red blood cells numbered 8,710,000, the white cells 28,000, and hemoglobin 94 per cent.

During his stay in the hospital (three days) two phlebotomies were done, removing 275 and 300 c.c. of blood respectively. This procedure relieved the dyspnea and lowered the blood-pressure from 190 to 165. The patient felt much better each time. While in the hospital the marked symptoms presenting themselves were dyspnea, cyanosis, and some edema of hands and feet. Fourteen hours after the last phlebotomy the patient became very dyspneic, with a weak running pulse. The patient died unexpectedly, gasping for breath. An autopsy was performed six hours after death by Dr. W. W. G. Maclachlan.

Autopsy Report. The body was that of a well developed, well-nourished adult male. There was much edema of the subcutaneous tissues, particularly at the ankles. The chest was well formed. There was a white scar on the prepuce, 1.5 cm. in length, at the right upper border of the corona.

Neck Organs. Near the bifurcation of the trachea there was some congestion of the mucosa, with a little frothy mucus in the lumen. The glands at the bifurcation were large, soft, anthracotic, with dull areas of congestion. These did not show evidence of tuberculosis.

Thorax. There were fibrous adhesions on both sides over the posterior lobes of the lungs and about 200 c.c. of clear amber-colored fluid was present in both pleural sacs.

Left Lung. The lung was much heavier than normal, weighing about 700 grams. The posterior surface of the lower lobe showed many fibrous tags of adhesions. The upper lobe was adherent to the lower by similar adhesions, but the posterior surface was smooth. The lung felt firm, particularly in the lower lobe, but considerable crepitation was still evident in it. The cut surface of the lung showed in the lower lobe a moist, glassy surface which, on pressure, exuded a frothy brownish-red fluid. The surface of the lower lobe had a dull, pinkish-gray color, with here and there ill-defined areas of varying sizes, which were even darker red, and

which, although glassy when scraped with the knife, appeared a little granular. Several minute pieces of the lung from these areas sank in water. Further, there were scattered through the lower lobe small, irregular round masses of white fibrous tissue. The small, round forms looked like tubercles, but were not typical, while the larger, irregularly shaped areas had a true fibrous appearance. The fibrous areas were abundant and gave the lung a marked increase in consistence, and further produced a somewhat mottled red and white color to the substance where these nodules were numerous. In places the distribution of the fibrosed areas had a bronchial arrangement, and, further, it seemed evident that some of the round masses were connected with the small bronchioles. The cut surface of the upper lobe showed about the same general appearance as the lower, only there was neither as much congestion nor edema, nor were the small fibroses as numerous, but they were still very evident. The bronchi of the lung showed much congestion of the lining and considerable frothy mucus. The peribronchial lymph nodes were anthracotic, but showed no tuberculosis.

Right Lung. The lung was enlarged and showed numerous fibrous tags over its posterior surface. The organ was generally firm, but crepitation could be elicited in most places. On section through the lung there was a general similarity of all the lobes. The amount of congestion and edema was much more evident in this lung. On squeezing it a brownish, frothy fluid escaped in large quantities. The upper lobe contained almost as much as the lower. The cut surface had a very glassy, slightly reddish color, with here and there some darker portions in the lower lobe, suggestive of hypostatic consolidation. Scattered through the lower lobe were numerous small areas of fibrosis similar to those in the left lung. Some of these were small and round, about 2 mm. in diameter, apparently having some relation to the bronchioles. Others were more irregular in their size and shape, although they never were large. The lower lobe was of much increased consistence. The upper lobe did not present so many areas of fibrosis, while in the middle lobe they were but rarely seen. The bronchi showed much congestion of the lining and a great deal of frothy mucus in the lumen. The peribronchial glands were large, anthracotic, rather soft, but showed no tuberculosis.

The heart showed no evidence of any valvular lesion, but the myocardium of the left side showed some hypertrophy. The aorta had occasional nodules of endarteritis and considerable wrinkling and puckering of the inner surface of the arch. The abdominal cavity was free from fluid. The liver, pancreas, and spleen showed nothing unusual, save some congestion. The kidney was pale, the cortex granular. The glomeruli were somewhat congested. The cortex was increased in width.

Microscopic. Lungs. Sections were made from various portions of the lung. By the naked eye one could discern small, solid masses occurring within the spongy tissue. These areas were at times directly beneath the pleura as well as in the deeper parts of the lung tissue. These tissue masses were found to be associated with the bronchioles. In these areas the normal structure of the lung was almost obliterated by a tissue reaction of an inflammatory nature. It was found that the stage of the inflammation was not the same in all parts, but in some a progressive reaction with an acute exudate was the prominent feature, while in others, stages of advanced granulation tissue were found.

The lung tissue between these foci of inflammatory reaction was of fairly normal character save for the presence of some congestion, a little edema, and occasional red cells within the air sacs. At times a dilatation of the alveoli suggested a compensatory emphysema; this, however, was never marked.

The punctate areas of inflammatory response were directly associated with the presence of a bronchiole lying more or less centrally within the areas of sclerosis. The inflammatory reaction always included the bronchioles with its surrounding connective tissue and a few of the neighboring alveoli. Thus there was an involved area resembling the nodules of inflammation in bronchopneumonia. In this case, however, the areas were much smaller, there being only a few alveoli surrounding the bronchioles which were attacked.

In places the bronchi and bronchioles were filled with red blood-cells, desquamated epithelium, and many polymorphonuclear leukocytes, lymphocytes, and plasma cells and fibrin. This subacute inflammation when present infiltrated the walls of the tube (bronchiole) and extended into the surrounding alveoli. In those areas where the desquamation of the lining epithelium was more marked there was a definite fibrinous exudate. This exudate showed evidence of organization by the proliferation and ingrowth of the connective-tissue cells of the wall. The muscle fibers were separated by the invasion of fibrous tissue from the surrounding stroma, which advanced by many prolongations into the lumen. In these areas of organization many new-formed and congested blood-vessels were seen. In other areas the bronchi and bronchioles contained a granular exudate in which there were occasional desquamated cells. Their walls had an irregular outline and appeared to be shrunken, and in one or two instances, more or less collapsed, obliterating almost half of the lumen. In these cases, where the walls approximated each other, many small strands of fibrous tissue were soon extending from wall to wall in a process of complete obliteration. Occasionally only half of the bronchial wall could be identified, with a dense mass of connective tissue lying along its side. The muscle tissue of the remaining portion of the wall could be readily recognized, while only an occasional strand was found in the adjoining connective tissue.

In places many bronchioles were filled with polymorphonuclear cells, fibrin, and granular debris. Along one border the lining epithelial cells were often missing while on the opposite side they were present in an irregular manner, beneath which there was a marked proliferation of the subepithelial connective tissue continuous with the fibrous tissue of the outer portion of the bronchial wall. The most prominent areas of fibrous induration were in the peribronchial portions. Here the true increase of the fibrous tissue was seen. At times it was cellular or again more dense in character, and of an adult appearance. The denser connective-tissue cells had immature characters. From this peribronchial connective tissue many extensions were seen in the septa of the neighboring alveoli giving them a thickened appearance, and at the same time diminishing the size of the alveolar cavity.

The alveoli also showed a variety of changes. They were, as a general rule, fairly normal looking, but uniformly small. In the immediate neighborhood of the bronchi and bronchioles the walls of the alveoli were definitely thickened by fibrous connective tissue. In the distal areas the alveoli contained a large number of red-blood cells and relatively few desquamated epithelial cells. Again, in other areas the alveoli were filled with cells of true inflammation of the polymorphonuclear, lymphocytic, and plasma-cell varieties. In these instances various stages of organization by newly formed fibrous connective tissue were observed. Various stages, from the early formation of fibroblasts and new bloodvessels to complete organization and obliteration of the alveoli by a dense fibrous connective tissue plug, were found.

In the intermediate alveoli or those situated more distantly from the bronchi and bronchioles a more normal appearance was maintained. However, there were relatively few in which no change had taken place, as they commonly contained red blood cells, desquamated epithelium, or had a slight fibrous increase in their wall. In places the epithelial lining of the alveoli and bronchioles was lifted from its basement membrane by a proliferation of fibroblasts extending toward the lumen. This fibrous tissue was continuous with the newly formed peribronchial fibroses. In the thick bands of fibrous tissue which course through the lung, as described above, many alveoli were found occupied or replaced by the growth of the firm fibrous tissue network. The infiltration of cells was not limited to the lumina of the bronchi and alveoli, but was also observed in the walls of these structures.

The bloodvessels and lymph vessels were considerably thickened. This thickening was due to a marked increase in the outer coats of the bloodvessels or their adventitial connective tissue. The sclerosis was quite loose and composed mostly of collogen fibrils and relatively few elastic tissue fibers. In the larger bloodvessels there was a slight increase in connective tissue of the intima.

Aorta. Sections of the aortic arch showed much change of the vessel. The intima was greatly and irregularly thickened by a laminated hyaline connective tissue. At the junction between the intima and the media there were a number of cellular collections of inflammation around small bloodvessels. Some of these vessels entered the deeper portions of the intima. The media was much affected by focal inflammation and degeneration. These focal areas were found in all portions of the media and consisted in central vessels surrounded by lymphocytes and plasma cells. About these areas the tissues showed degeneration. In places the musculature and elastic tissue were completely interrupted. By elastic-tissue stain one could distinguish various grades of degeneration, with complete destruction of elastic fibers. The adventitia was much thickened by fibrous tissue in which elastic fibers were almost wanting. The vasa vasorum showed thickening of their walls, particularly of the intima, with narrowing of their lumina. Occasionally, lymphocytic and plasma-cell infiltrations were observed around the vessels of the adventitia.

Liver. The liver lobules were fairly well preserved and the columns were quite regular. There was some lymphocytic infiltration about the portal system, with a slight increase in connective-tissue cells. A greater number of leukocytes were seen scattered throughout the liver than are normally seen in the sinuses. Two small areas of focal necrosis with lymphocytic infiltration were observed. In some instances the sinuses were rather deeply congested, but this was not uniformly present.

Kidney. Sections of the kidney showed the cortical tubules enlarged. These tubules were lined by an irregular, low epithelium which had large poorly staining nuclei and finely granular or nebular cytoplasm. The lumina of these tubules contained granular débris. The glomeruli were all enlarged and surrounded by a thin capsule. They showed no evidence of acute inflammation, but had in some instances a rather degenerated appearance. In a few instances a few polymorphonuclear leukocytes were seen in the glomeruli. The capillaries in the glomeruli were patent and in some instances concongested. Elsewhere, again, there was evidence of bands of inflammatory reaction running through the cortex and involving the glomeruli and tubules. Within these areas there was an excess amount of connective tissue. This was infiltrated with lymphocytes, polymorphonuclear leukocytes, and plasma cells. The involved glomeruli showed a thickening of the capsule with hyaline change. Synechiæ were common, and where found the glomeruli were involved in the same change observed in the capsule. The hyaline change gradually progressed in the capsule until a whole glomerulus was obliterated.

Sections of the heart, pancreas, spleen, and prostate showed no definite pathological change.

To briefly review the foregoing case the following are the main facts: A man, aged thirty-nine years, with an antecedent history of lues, was accidentally subjected to the inhalation of irritating gases. At the time of the accident he suffered nothing more than a sever fit of coughing. Three days later dyspnea suddenly developed, increasing continuously until the time of his death, three weeks later. During his illness his most marked clinical manifestations were dyspnea, cyanosis, and some edema of the feet and hands. Clinically, no pulmonary consolidation could be discovered, but the chest examination indicated mainly a bronchial involvement. At autopsy numerous small fibrous foci were observed in the lung tissue, suggesting miliary tuberculosis, but not showing any evidence of necrosis which marks these lesions. The microscopic analysis showed the presence of inflammatory reactions in and about the bronchioles, accompanied by a process of organization. In this way it differed from a process of bronchopneumonia, to which, however, it had the closest resemblance. The lesions had no relation to tuberculous infection. Their remarkable feature lay in the process of resolution. The early acute inflammatory processes resembled an exudative bronchiolitis in which leukocytes, fibrin, and epithelial, lymphoid, and plasma cells constituted the main bulk of the exudate. The inflammatory reaction, however, was not alone confined to the development of an exudate lying within the ramifications of the bronchi, but there was a tendency to bring about tissue change in the neighboring structures. The bronchi showed more or less desquamation of their epithelial lining and their walls and surrounding connective tissue were stimulated to proliferate. In all areas there was evidence of connective-tissue growth whereby the outer portion of the bronchial wall became thickened, while a granulation tissue formed bulbous ingrowths into the lumina. Thus bronchi were found which were narrowed partly by the shrinkage of the peribronchial fibrosis as well as by organic plugs filling the lumen. Associated with these organizing inflammatory reactions, more or less of the surrounding air sacs were involved in a similar process. Numerically the number of air sacs involved were relatively few, as there were wide stretches of lung tissue in which the inflammatory process had no effect. The presence of red-blood cells in the outlying alveoli was a terminal condition associated with the intense dyspnea accompanying the fatal outcome. The involved alveoli were disturbed by a fibrosing process very similar to that of the bronchioles. A thickening by fibrous tissue involved the alveolar septa while an ingrowth of granulation tissue occluded to a greater or lesser degree the air sacs. To some extent the sclerosis involving the bronchi and neighboring air sacs also encroached upon the lymphatic channels and bloodvessels in the surrounding trabeculæ.

A number of cases of bronchiolitis obliterans have been reported

in the literature. Clinically and pathologically they have a close similarity. In all of them dyspnea and cyanosis is the most important feature, and in many this is of sudden onset. Etiologically, however, the reported cases may be divided into three groups: In the first group are the cases of apparently spontaneous origin in which no antecedent history indicates the reason for the organizing inflammation. Such cases were reported by Lange (Case I), Karwicka and an unreported case by Cobet, of Marburg. These cases bear a striking similarity in their sudden onset and absence of preceding illness. Dyspnea is usually the first indication of illness, and rapidly progresses with fatal termination in forty-eight to seventy-two hours. No definite etiology has, as yet, been determined for this group. Group two includes the cases in which a definite history of preceding bronchopneumonia has gradually led to an organizing pneumonia of the lobular type. Cases of this kind following measles, chronic bronchitis, and foreign bodies in the bronchus have been reported by Lange, Vogel, Müller, Wegelin, Hart, Ribbert, Pernice and others. In this group the process of organization is not unlike that observed in the organizing pneumonia of the lobar type. A considerable study and discussion have been made upon the factors leading to the development of granulation tissue in the various forms of infectious pneumonia. Just what conditions modify the responses in the lung which, under certain conditions, lead to complete resolution, while others bring forth granulation tissue, is still far from clear. The third group, of which the case here reported in one, consists of cases in which individuals have been subjected to the inhalation of irritating gases. Fraenkel, in 1902, studied a case of bronchiolitis obliterans in a man, aged twenty-five years. During his work as a brass-moulder he was accidentally subjected to the fumes of nitric acid. Dyspnea and cyanosis became marked on the third day, and he died at the end of three weeks. Edens reported a similar case of inhalation of hydrochloric acid and sulphuric acid. Here, again, after the initial sense of choking, dyspnea became a marked feature on the second day. Gradually the dyspnea improved and the patient was well at the end of a month. Edens reported a third case in which the patient suffered from the inhalation of ammonia. To this third group we must add our own, which is very like that reported by Fraenkel.

It is probable that a pathological distinction cannot be made between the lesions found in the three groups. The fibrosing process has in all of them a close relation to an inflammation in the bronchial walls. There is some variation in the character of the exudate in the different cases, but the process of repair appears to be common in all. Wassiljew makes a distinction between the organization of an exudate of a preceding acute inflammation and the development of a granulation tissue arising from the bronchial wall or septa of the alveoli. Such a classification cannot, how-

ever, be applied to all of these cases, as some are found with evidence illustrating each mode of fibrous-tissue production. In our own case the growth of bulbous masses of granulation tissue was more prominent than the ingrowth of fibroblasts through the meshes of an antecedent fibrinous exudate.

The reports upon fibrosing bronchitis have mainly dealt with a study of the origin of the connective tissues. Some attempt has been made to explain the reason for the abnormal growth of fibrous tissue as compared with the usual outcome of inflammatory processes in the parenchyma of the lung. Up to the present these explanations have not been entirely satisfactory. Undue stress has been placed upon the differences between the growth of the connective tissues during the organization of an inflammatory exudate and its apparent spontaneous proliferation from connective tissue containing areas. These points of differentiation were a prominent part of the discussion at a time when it was believed that the inflammatory cells of an exudate gave rise to the fibroblasts of organization. When, however, at the present time it is accepted that the fibroblasts appearing during the stage of repair of an inflammatory process have their origin from fixed connective-tissue cells of the injured area, the polemic upon the differences of connective-tissue growth with or without the presence of fibrinous exudate no longer has such an important meaning. Karwicka, Edens, Lange and others have all shown that the fibrous tissue found in obliterating bronchitis has its origin from a similar tissue in the walls of the bronchioles. At times it appears to arise from the submucosal tissues, while in other instances, and particularly when the reaction is more extensive and the peribronchial stroma is in active proliferation, the intratubular masses appear to originate from these outlying structures. The observation has been repeatedly made that the proliferating peribronchial tissues break through the muscular ring and present themselves in a warty growth inside of the bronchi. That this ingrowth actually occurs may be seen in the presence of anthracotic pigment carried inward with the stroma from the peribronchial deposit. A similar overgrowth of the connective tissue also appears within the air sacs. Here, however, one also finds evidences of organization of exudate as is commonly observed in areas of aseptic repair.

Another point in regard to the inflammatory process of the bronchial wall is the sequence of events as may be observed in those cases. True it is that observations have not been made upon the lung reactions from the time of injury until death; nevertheless, in these peculiar cases various grades of the reaction may be observed in the same specimen. It is probable, as indicated by the clinical manifestations, that congestion and edema are among the early effects upon the bronchi and their branches by the inhalation of irritant gases. A serous flow from the mucosal surfaces leads to

the expectoration of considerable quantities of thin sputum. Following this a desquamation of the epithelial covering denudes much of the bronchial wall. In one case reported by Edens the exfoliation of the mucosa permitted the patient to expectorate partial casts of the bronchial tubes. Such an extensive desquamation is unusual. Microscopically, however, all of the cases showed fairly large areas from which the mucosa had been removed. At these points the bronchial wall becomes subject to a more deeply infiltrating inflammatory process than those areas in which the mucosa remains intact. Moreover, it is at these denuded sites where the proliferative reaction of the connective tissue is prone to occur. It is probable that the unequal distribution of the injury upon the bronchial wall is in part dependent upon the presence or absence of layers of mucous secretion. The finding of greater damage in the bronchioles as compared with the lung tissue probably results through spasm of the distal portions whereby the gas is not admitted into the alveolar structures. This is similar to the spasm of the esophagus observed in children upon accidentally drinking strong caustics. In the latter instance the caustic fluid does not reach the stomach, but is momentarily held through spasm of the cardia in the lower portion of the esophagus. The alveoli of the lung, which show a process of organizing inflammation, appear to be involved because of their proximity to the damaged bronchioles.

Thus the bronchioles directly influenced by the acrid gases suffer desquamation of their epithelium and have their deeper tissue injured by the primary noxious agent. The reaction in these tissues is of stimulating kind, whereby a varying amount of migratory exudate permeates their interstices and also whereby the irritant acts as a stimulating factor upon the connective tissues. Whether a further stimulus is induced through the presence of bacteria and their toxins or by the effect of products of decomposition is difficult to say. It appears, however, evident that the primary irritant has in itself a peculiar effect in leading to tissue overgrowth.

It is evident that the fibroses appearing under the conditions as we have described differ materially from those arising in the lung through other agents. The fibroses associated with tuberculosis, actinomycosis, and aspergillosis of the lung appear in localized areas of tissue destruction in an attempt to repair limited damage. The stimulation for the growth of connective tissue under these conditions is not greater than the demand necessary for such repair. Similarly, the fibroses occurring in and about the lymphatics of the lung as the result of the presence of foreign materials (coal dust) is limited in its extent and relative to the irritating effect of the foreign material. Infiltrating fibroses are sometimes seen in the periphery of the lung advancing from areas of chronic pleurisy, but these again are usually localized and in proportion to the extent and chronicity of the infectious and inflammatory products. More

closely allied to the proliferation observed in obliterating bronchitis is the organization of unresolved pneumonia. Some comparable features are here observed. Under these conditions the alveoli filled with exudate show more or less desquamation of their lining epithelium. An irritant differing from that usually present in lobar pneumonia stimulates an interstitial reaction in which the connective-tissue cells are also involved. If their response is one of proliferation the alveolar sac is invaded and it may be occluded. The presence of exudate assists in directing the growth of the fibroblasts and in producing synechiæ. It has been a not uncommon observation that cases of indurative pneumonia also show some bronchial involvement. A series of these cases was studied by Wassiljew, who believed that the bronchial lesion was independent of the changes in the alveoli, though probably the result of a common cause. He found the intratubular fibrous tissue of the nature of a true granulation tissue. An interesting experiment was undertaken by him in which a bronchopneumonia was induced in dogs and rabbits by injecting a 2 per cent. solution of agar into the bronchi. By this means he was able to induce a fibrosing process partially occluding these tubes. These experiments, however, simulate more closely the induction of fibrous-tissue proliferation in the vicinity of foreign bodies.

The intense clinical manifestations of dyspnea are referable to the stenosing process in the bronchioles. Not alone do the bronchioles suffer obstruction through the presence of fibrous plugs, but the narrowed tubes tend to accumulate masses of mucus at the points of constriction. Moreover, it is probable that the spasmodic attacks of dyspnea result from an increased irritability and convulsive muscular contractions of the bronchioles.

It would be interesting to know whether the late effect of the gas-poisoning upon the European battle-fields is of the nature of a fibrosing obliterative bronchiolitis.

I wish to express my sincere thanks to Dr. Oskar Klotz for his assistance in the preparation of this paper.

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DIABETES ASSOCIATED WITH HÆMOCHROMATOSIS

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TROUSSEAU early in the eighteenth century referred in his clinical lectures to an autopsy upon a diabetic having a bronzing of the face, an almost black discolouration of the penis, and a greatly enlarged and cirrhotic liver. Troisier in 1871 described a similar case under the name "Diabète sucre". Hanot and Chauffard in 1882 and Hanot with Schachman in 1886 have been given the credit by most authors for first describing the disease in their reports of two cases and naming the condition "Diabète bronzé". They believed that the diabetes was the primary manifestation and that subsequently the liver cells were stimulated to an increased production of pigment.

Many authors have since commented upon the subject, and different views have been advanced. The discussions have centered about the questions pertaining to the sequence of events in the disease. One of the important points considered was whether there were two somewhat similar bronzing diseases, one associated with cirrhosis of the liver and the other with diabetes mellitus. Much has been learned of the nature of the process in each by the many clincial and pathological studies. The pathological processes leading to a deposit of iron-containing pigment in organs, many times greater than that normally found, has been an especially difficult problem for solution, partly because the blood in which one would expect to find signs of red blood cell destruction, indicates no more than a slight anæmia.

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A review of the literature concerning iron-pigment deposits, a discussion of the hypotheses of the many authors and the hope of suggesting some new ideas on the subject (besides the fact that this is but the ninth case reported in the United States), is sufficient reason for bringing forward this report.

I think it can be fairly established that there are three cardinal features of the advanced cases, namely, pigmentation of the viscera and usually of the skin, cirrhosis of the liver of a portal or atrophic type, and diabetes mellitus which dominates the clinical picture of the later stages. These clinical and pathological features constitute "bronzed diabetes".

Simple hæmochromatosis without diabetes has been described a number of times (13, Potter and Milne) and it is interesting to note that in cases so described, cirrhosis of liver and other organs were also present. A minor type of hæmochromatosis has likewise been observed in a variety of diseases in which, however, the evidence of a primary blood destruction was an outstanding feature. Some of the reported cases of simple primary hæmochromatosis show that the cause of death was occasioned by an intercurrent disease, such as typhoid fever (Opie), and tuberculous peritonitis (Sprunt). It is, therefore, possible that the fatal complication prevented the development of the typical picture of bronzed diabetes before death. However, according to the observations by Anschutz on six cases of bronzed diabetes, it has been shown that glycosuria may be a very variable sign disappearing for certain periods during the disease. Letulle reported a case in which the glycosuria was absent for two months and then reappeared. Other authors have likewise noted a varying glycosuria during treatment or just before death.

I am indebted to Drs. Nettleton and Mercur for the clinical data and for permission to report the following case.

Case History: Mr. W. M. D., aged forty-six, plumber by occupation.

Family History: Father died at the age of seventy-one of cancer of the tongue; mother died at the age of eighty-one of cerebral apoplexy. Three brothers are living and well. One brother died at the age of twenty-seven, the cause of death being unknown. Two sisters are living and well.

Personal History: He has had the usual diseases of childhood. He was a heavy drinker from about 1890 to 1900, but since 1900 he has had periods of total abstinence with an occasional spree at which time he drank large amounts of whiskey. He has suffered a good deal from digestive disturbances and first came under observation in 1902 for the relief of indigestion. He complained at that time of eructation of gas and food and of feeling tired and listless. He slept well but was tired on awakening. During this illness, he lost eighteen pounds in six months. At this time he had pain and tenderness in the epigastrium. Subsequently for a number of years he suffered from gastric and intestinal indigestion. Attacks of "grippe" were frequent, yearly from

1890 until 1897, and sometimes twice a year. He also had various so-called rheumatic affections and lumbago. In 1896 he suffered an attack of gout. In 1902, until August, 1913, he had many recurrences of hyperchlorhydria.

From the time he came under observation he was never robust. His appearance was that of a prematurely old man, his hair having turned quite gray, which, however, was a family characteristic.

Present Illness: From the time he came under observation there was no indication of renal or liver disturbance until 1912, when the urine showed a few hyaline casts and a fairly well marked reaction for indican. The specific gravity was 1025. The indican cleared up after several weeks.

In July, 1913, there was a large amount of indican, which disappeared after a prolonged treatment and rest. On August 22nd, when at least semi-weekly examinations were being made, the first appearance of glycosuria was noted. This glycosuria soon became excessive, and in December he had become bed-ridden. From the time he was bed-ridden until his death, almost daily estimations of the total percentage of sugar were made by Benedict's method. Urea was also estimated from time to time.

SUGAR ESTIMATIONS

August 22, 1913	Trace.
" 23, "	No Sugar.
" 25, "	Slight.
" 26, "	Slight.

Dr. Nettleton was out of town for a period and records were not kept of the amounts of sugar found.

December 15, 1913	3·0%	December 28, 1913	2·9%
" 16, "	4·6	" 29, "	2·7
" 17, "	4·5	" 30, "	0·2
" 18, "	3·10	" 31, "	0·3
" 19, "	3·18	January 1, 1914	0·5
" 20, "	1·9	" 2, "	2·3
" 21, "	2·2	" 3, "	7·0
" 22, "	2·1	" 4, "	1·0
" 23, "	3·1	" 5, "	2·0
" 24, "	3·1	" 6, "	2·4
" 25, "	2·9	" 7, "	2·8
" 26, "	2·6	" 8, "	2·8
" 27, "	2·8	" 9, "	0·2

At no time during the course of the diabetes mellitus was the urine sugar free, the nearest approach was on December 30th when the patient had a "green day" with much nausea and vomiting. From December 15th, the patient was on strict carbohydrate free diet.

The total quantity of urine varied from 2150–4200 c.c. until January 8th, when there was almost complete suppression until death on January 12th. Acetone and diacetic acid were present in very large quantities and were constantly observed from the early part of December. Ammonia was estimated. The minimal total was recorded on December 21st at 3·029 grammes and the maximum on January 3rd at 5·0 grammes.

The patient was poorly nourished and became greatly emaciated. At no time during the course of this disease was an enlarged liver observed and the spleen was never palpable nor enlarged on percussion. There was tenderness over the liver and in the epigastrium.

The following autopsy report is taken from the records of Professor Oskar Klotz, to whom I desire to express my thanks for the assistance rendered me during the course of the work.

AUTOPSY

The body was that of a thin and much emaciated man appearing considerably older than the stated age. The skin surfaces were quite pale and rather yellow. Post-mortem rigidity was present and there was some lividity of the dependent parts. The hair was quite white, the eyes were sunken and the tissue over the cheek bones was sparse. The neck was long and thin, and the supraclavicular fossæ were quite deep. The chest was long and narrow, while the antero-posterior diameter was shallow. The abdomen was flat. There was no evidence of œdema of any of the tissues.

Thorax: The thoracic cavities were quite clear. There was no excess fluid in either cavity and neither lung presented any adhesions. The pleural surfaces were clear, shiny, and quite pale.

Lungs: Both lungs crepitated in all their parts. The lung tissue was quite soft and there was no evidence of consolidation in any portion. Foci of tuberculosis were not evident. There was a little hypostatic congestion along the posterior border of the right lower lobe. There was relatively little anthracosis in the lung tissue. Some of the lobules were bordered by lines of black pigment.

Heart: The pericardial sac contained a small quantity of clear yellow fluid. The pericardial surfaces were clear and shiny. The heart was very flabby and moulded itself in various positions when placed upon a flat surface. Both ventricles were in partial diastole. Partially coagulated blood was present in all cavities. The heart was rather globular in shape, the apex being rounded and being formed by the lateral border of the left ventricle. The tip of the left ventricle appeared to be drawn upwards on the right side. The epicardium contained a fair amount of bright yellow fat. The heart valves were fairly normal save that there was a slight thickening of the free border of the tricuspid valve as well as some thickening of the insertion of the aortic valves. The valve leaflets, however, were free and apparently competent. There were a few fatty spots upon the posterior surfaces of the free mitral cusp. The heart muscle was light in colour and of a yellowish red appearance. The muscle tissue of all parts was extremely flabby and quite easily broken. The cut muscle was rather mottled and showed some distinct yellow areas on the cut surfaces. Some of the papillary muscles of the left ventricle showed a distinct thrush breast mottling. The coronary arteries showed some yellow plaques irregularly distributed along the main vessels. This was more prominent in the coronary. The muscle of the ventricle appeared thinner than normal and the cavity of the left ventricle was enlarged. The foramen ovale was closed.

Aorta: The base of the aorta was quite thin and elastic and showed a few fatty streaks just above the aortic ring. The aortic wall showed no sclerosis. It was observed, however, that the larger vessels arising from the abdominal aorta, and particularly the superior mesenteric and splenic artery showed considerable sclerosis and rigidity of their walls.

Abdomen: On opening the abdomen very little fat was found over the abdominal parietes. This fat was quite lobulated and of a rather dark yellow appearance. The abdominal muscles were thin and appeared atrophied. The peritoneal surfaces were all clear and there was no excess fluid in the abdomen. The coils of the small intestine were free and only slightly distended with gas. There were no peritoneal adhesions. The great omentum was very thin and contained a little fat. The transverse colon was distended with gas and formed a large V-shaped loop whose lower border reached 4 cm. below the umbilicus. The liver projected 5 cm. beyond the tip of the xyphoid but the border did not extend below the costal margin on the right side. There were no adhesions in the vicinity of the liver. The diaphragm arched to the fifth rib in the right nipple line and to the sixth rib in the left nipple line. In the vicinity of the

duodenum there were no adhesions or any evidence of an abnormal process. The stomach was quite free in its position.

Stomach and Intestines: Nothing of particular note was observed in connexion with the gastro-intestinal canal. Evidence of inflammation or bands of adhesions were wanting. The bile papillæ in the duodenum appeared normal and quite patent. There was no pathological process associated with the ampulla of Vater. The appendix showed some constriction and fibrosis in its upper one-third with slight dilation in the middle third in which an enterolith was found. There were no adhesions about the appendix.

Liver: The organ was above normal size. Both lobes were well devoloped, the left appearing larger than usual. The capsule of the liver was quite thin and transparent. Along the lower border of the left lobe the surface of the liver was rather granular. There were two vertical grooves extending over the dome of the right lobe for a distance of about 12 cm. These grooves were parallel. The liver substance was brown in colour and did not have the usual red or reddish gray appearance of liver tissue. The colour resembled that of iron rust. The cut surface of the liver was quite granular and although the liver lobules were not distinct, the markings of the portal system were more prominent on account of a glassy fibrous tissue outlining them. The liver tissue was quite firm and was not readily broken. When cut with a knife the tissue appeared tough, and the cut surface was a bright brown and quite granular. The bile channels within the liver showed nothing of note. The gall bladder contained a rather dark bile but its walls were thin and normal. The bile ducts extending to the duodenum were healthy and evidence of stone, inflammation, or tumour was wanting.

Pancreas: Measured 17 x 4 x 3 cm. The pancreas was carefully dissected out with a portion of the duodenum attached. The pancreas was of good size and showed no evidence of atrophy in the gross specimen. Over the surface of the pancreas there were seen a number of small pinhead-sized white spots, which, on close examination, were found to be fat necroses. Several of these spots were also seen within the organ. The tissue surrounding the pancreas appeared quite normal. The pancreas was quite firm and on section the lobules were unusually distinct. The lobules were separated by definite and prominent fibrous tissue trabeculæ. This fibrosis was diffuse and not isolated to any particular region of the organ. The colour of the pancreas was striking and resembled that previously noted in the liver. It was of a decided bright brown or rusty character. The pancreatic ducts were not dilated and there was no evidence of obstruction or other pathological change in these passages. Some of the lymph glands in the vicinity of the pancreas were slightly pigmented while other lymph glands found near the head of the pancreas showed a very decided rusty colour. The glands though a little enlarged, showed no macroscopic evidence of fibrosis.

Spleen: The spleen was about normal in size. The capsule was thin and somewhat wrinkled. The tissue felt rather flabby and on section the organ was quite dark with occasional rusty areas. The Malpighian bodies were visible, the pulp substance was not easily broken and there was no evidence of definite fibrosis to the naked eye.

Left Kidney: The kidney was considerably larger than normal. The posterior border was rounded and of a hog-back character. The capsule was quite thin and peeled easily. The outer surface of the kidney was very pale, and rather grayish white. On section the cortex and medulla were sharply demarcated. The cortex was quite wide and of light colour and showed a rather granular appearance with streakings of red and gray. Many of the glomeruli were visible as congested dots. The pelvis and ureter were without change.

Right Kidney: The organ was similar to that of the left showing general enlargement and the light colour of the cortex. The cortex appeared wider than usual and showed similar streakings as in the left.

Adrenals: Both adrenals were of normal size. The cortex was thin and of a bright yellow colour. The medulla was soft and dark. In the medulla the tissue had a rather rusty brown apearance. The medulla was so soft that it was readily broken during removal.

Thyroid Gland: The thyroid was small, both lobes being smaller than normal. The tissue was of a dark meaty character and showed relatively little colloid. There was no evidence of fibrosis.

Anatomical Diagnosis: (Bronzed diabetes): fibrosis of pancreas; fat necrosis of pancreas; hæmochromatosis of liver, pancreas, heart, spleen, adrenal, thyroid and lymph glands, fatty degeneration of heart; brown atrophy of heart; dilatation of heart (right and left ventricles); peripheral arteriosclerosis; portal cirrhosis of liver; chronic parenchymatous nephritis.

A brief review of the outstanding points in the case both from the clinical and pathological side would indicate the following conditions. The patient was an adult male forty-six years of age; he was a plumber by occupation, and had been a heavy whiskey drinker. From 1902 until his death he suffered many gastro-intestinal disturbances and loss of weight. There was pain and tenderness in the epigastrium, but the liver was not obviously enlarged. The spleen was not palpable. The patient yearly suffered attacks of grippe and had numerous attacks of neuralgia, rheumatism, and lumbago. On August 22nd, 1913, there was found a trace of sugar in the urine which soon became excessive and the patient rapidly weakened. Acetone and diacetic acid were found in December, 1913, and the patient died in semi-coma with a terminal decrease in percentage of sugar and almost suppression of urine on January 12th, 1914. At no time was the urine sugar free. At autopsy there was found hæmochromatosis of liver, heart, spleen, adrenal, thyroid and lymph glands; portal cirrhosis of liver and fibrosis and fat necrosis of the pancreas. The pathological findings, therefore, were typical of the so-called bronzed diabetes.

Portions of different organs were fixed in Zenker's solution and in formalin for microscopical study. Microscopic sections were by the paraffine method and stained with eosin and methylene blue, hæmatoxylin and eosin Van Gieson's method and by lithium carmine and picric acid. Other special connective tissue stains were used. For iron pigment, we found that Perl's method was quite unsatisfactory. Nishimura's modification of Perl's method was substituted and our results show that this procedure is much superior for the demonstration of iron in tissues. Briefly Nishimura's test for iron pigment is as follows: formalin fixed sections are immersed in a strong solution of ammonium sulphide for one hour. Washed thoroughly in distilled water. The sections are then placed in a mixture of 2 per cent. potassium ferrocyanide and 1 per cent. hydrochloric acid for twenty minutes. Finally place the sections in 0·5 per cent. hydrochloric acid until blue (twenty minutes to one hour). Wash in water. Counterstain with hæmatoxylin and eosin or lithium carmine differentiated by picric acid and mount in balsam.

MICROSCOPICAL

Liver: The sections of the liver showed the well preserved lobules or aggregations of lobules distinctly defined by an excess amount of connective tissue in the periphery. However, a very striking feature was the presence of a large quantity of golden yellow

pigment, as fine granules or in coarse masses in all portions of the liver. This pigment was present within the lobules and was found within the liver cells as well as in the interstitial tissue. The amount of pigment within the liver cells varied from a fine sprinkling of a few small yellow granules to a crowded condition in which the substance of the cell could not be recognized. However, there appeared to be a tendency to a peripheral arrangement of the pigment in the cell. The lining cells of the bile capillaries and large bile ducts also contained the pigment.

The interstitial tissue of the portal systems was markedly increased. The greatest amount of pigment was in the periphery of the lobules in the area occupied by the portal cirrhosis. In so far as the liver parenchyma itself was concerned there was more pigment in the central portion of the lobule than in the peripheral parts. In the sinusoids a little free pigment was noted. Kupffer's cells were well filled with pigment granules. One would be led to infer that a part, at least, of the pigment present in the fibrous tissues of the portal areas had accumulated as a result of the death of some of the liver cells. In the muscle fibres of the walls of the blood vessels, in the endothelial cells of the vessels and of the perivascular lymph spaces a moderate amount of pigment was demonstrated.

Throughout the section the central portion of the liver lobule showed an adenomatous hyperplasia. These areas were small, round, and contained but a slight amount of pigment.

Sections stained with sudan showed only occasional fat droplets within the liver cells. There was no evidence of a fatty degeneration. Nishimura modification of Perl's test showed a prussian blue colour in the pigment throughout the section.

The areas of fibrosis showed a mature connective tissue with but slight progressive reaction in which lymphocytes were found. The fibrosis was distributed in a manner parallel to the direction of the vessels in the portal system. In part, it appeared that the deposit of pigment in these areas was within lymphatic spaces and at times within spindle-shaped fibroblastic cells. The fibrosis was not arranged concentrically about the pigment masses. Many pseudobile ducts were noted within this new connective tissue.

Pancreas; The lobules of the pancreas were well retained and separated from each other by strands of connective tissue, which, in places, was in excess. It cannot be said, however, that the excess of fibrous tissue was particularly of an interlobular type. More marked evidences of fibrosis were present within the lobules. There was no lymphatic infiltration in the fibrosed areas. In these situations curious patches of connective tissue occupied each lobule and pervaded the surrounding tissues in a stellate manner. These areas of fibrosis were also the site of an accumulation of a rusty yellow pigment. This pigment was found within the glandular cells of the neighboring alveoli as well as in the clefts of the mature connective tissue. Nearly every secreting cell of the pancreas contained pigment in varying amounts, more marked in the periphery of the lobule.

The pancreatic ducts showed no evidence of dilatation. It was noted that the epithelial lining of these structures was for the most part wanting or present in accumulated debris. These cells were not pigmented.

The islands of Langerhans were almost entirely obliterated. A few partially preserved islands were found. The majority of them were involved in fibrosis showing much capsular thickening and some hyaline change of the fibrous tissue. There was some pigmentation of the islands.

Several areas of fat necrosis were found in frozen sections. These areas were quite apart from the tissue involved in fibrosis or pigment deposit. A slight infiltration by lymphoid cells was seen about some of these areas of necrosis.

Lymph Gland: (Near Head of Pancreas): This gland showed quite a remarkable appearance. The whole structure with its capsule was permeated by a rusty yellow pigment which was deposited in coarse granules of irregular shape. Some of the larger pigment masses showed a granular centre with a homogeneous laminated outer struc-

ture. The pigment was present within some endothelial cells, but for the most part, it appeared to lie in the clefts of a new formed connective tissue.

The gland had lost its normal architecture and the lymph follicles had disappeared. In their place a connective tissue permeated the entire structure. The older areas of fibrosis were of a hyaline character. The lymph sinuses were quite patent and contained cells filled with pigment. On the other hand, the large lymph channels showed the presence of precipitated albumen while free pigment and pigmented cells were entirely wanting in them.

Rather curious structures were found in various portions of the lymph glands. These consisted of jointed strands showing branches and looking not unlike coarse mycelial threads of some moulds. These structures did not stain well with hæmatoxylin, and were Gram negative. Commonly they were grouped together and fibrosis was usually evident in their vicinity.

Sections of the lymph gland when treated with Nishimura's method gave a marked iron reaction. The mycelial like strands also took on the prussian blue colour.

Intestine: (*Duodenum*): Sections of the duodenum showed a normal looking structure. There was no evidence of inflammation. In the mucosal folds a slight amount of a yellowish iron-containing pigment was seen in the interstitial tissue. The epithelial cells did not contain pigment, nor was there any of it present in the deeper structures of the bowel wall.

Heart: The heart muscle was very pale and the fibres were quite narrow. Fragmentation and segmentation of the muscle fibres were evident in all portions of the tissue examined. There was no evidence of an inflammatory reaction or of old fibrosis. The arteries in the muscle tissue showed slight sclerosis. On the other hand, the muscle fibres were loaded with a brown pigment which had accumulated within their substance. This pigment was well retained even after alcohol treatment. This pigment was particularly evident in the vicinity of the nuclei and was arranged in a peculiar wedge-shaped manner towards the ends of the fibres.

Besides this another form of pigment was present in the myocardium. This was observed in the interstitial tissue between the muscle fibres. In the vicinity of the small arterioles a number of oval perithelial cells were not uncommonly seen containing much of this pigment. The pigment was much coarser and darker than that within the muscle fibres. With the test for iron, two pigments were demonstrated. One gave a positive reaction, the other was negative. The latter was deposited in the muscle fibres and corresponded to the nature and distribution of the pigment of the brown atrophy. All of the remaining pigment both within the muscle as well as in the interstitial tissue was iron-containing.

Adenal: The adrenal cortex contained very little fat. The inner zone of the cortex stained poorly and the arrangement of the cells was not as regular as usually found. The pigmented zone of the medulla was well marked. There was no evidence of an inflammatory infiltration. In the outer zone of the cortex, close beneath the capsule were found a number of patches of pigment deposit. These consisted of a brownish yellow coarse and granular pigment. The deposits were within the cells of the adrenal columns. In some places an excess amount of fibrous tissue invaded the cortex from the capsule. The pigment deposit in the outer portion of the cortex was quite distinct from the pigmented cells of the medulla. The iron reaction showed all of the pigment, except that in the medulla, to be iron-containing.

Thyroid: The section of the thyroid showed a rather congested tissue in which the alveolar spaces were small. For the most part, the alveoli consisted of small gland-like structures devoid of lumina. Colloid was present only in slight amounts. The alveoli were not enlarged, and it was only seldom that the epithelial lining was thrown into folds. The epithelial cells were, for the most part, cubical. Many of the alveoli contained a fine pink-staining granular material.

An interesting feature was the presence of a granular yellow pigment similar to that previously described, which was present in the epithelial cells lining the alveoli. In the interstitial tissue which was slightly increased in amount there was moderate

pigmentation. The pigment lay in fibrous tissue cells. Again some slight pigmentation was noted in the endothelial cells lining the perivascular lymph spaces. Free pigment in the alveoli was only occasionally seen. There were, however, a few masses of desquamated epithelial cells with pigment lying in the lumina of the glands. This pigment gave a positive iron reaction.

Spleen: The Malpighian bodies were well defined. The central arteries showed some hyaline degeneration of their walls. The pulp substance was quite congested and in the walls of the sinuses were irregular deposits of pigment which had been phagocyted by the large endothelial cells. There was some evidence of fibrosis, but it did not appear that the tissues of this organ were particularly active in the process of regeneration or destruction of red blood cells. In the trabeculæ there were some iron deposits, the pigment being held in connective tissue cells. Likewise some granules of pigment were noted in the muscle cells of the large vessels. The pigment gave a positive iron reaction.

Kidney: There was considerable change in the cortex of the kidney. For the most part, this change was in the parenchymatous portion, there being little or no reaction in the interstitial tissue. The glomeruli were large and their capsules widely dilated, with, in many instances, a vacant space between them and the glomerulous. The glomerular capsule was not thickened. The convoluted tubules were large, the epithelium stained poorly, and the individual cells were of irregular size and shape. Many of these tubules contained a debris. A number of loops of Henle were found to contain a slight amount of yellow granular pigment. The amount of this pigment was relatively small. It was absent from the convoluted tubules and from the glomeruli. The sudan stained specimens showed an unusual amount of a fatty degeneration of all the tubules of the cortex. Likewise a considerable amount of fat was present in the collecting tubules of the medulla. In the cortex the fat was present at the base of the epithelial cells and appeared in small clusters of yellow globules. The stained tubules were sharply outlined by the amount of fat present in the peripheral portion.

The diabetes in the case reported was of very severe character, the process lasting from August 22nd, 1913, to January 12th, 1914. It was associated with the fibrosis of the pancreas and islands of Langerhans. The fibrosis in the liver and elsewhere could not have resulted in such a short period as indicated by the diabetes. Acetone and diacetic acid appeared early in the diabetes and the patient died in mild coma. Death in other cases usually occurred within a year or very little over.

From the literature of this very interesting pathological process, one can classify the views of the different authors on the etiology of bronzed diabetes into five large groups. (1) Many regard a primary blood destruction as the cardinal factor in the production of pigmentation and fibrosis; (2) another group of observers take the opposite point of view and lay no stress upon changes going on in the blood, but believe that there is a retention of the normal pigments; (3) others lay stress upon the abnormal metabolism of the cells, (a) disturbed chromogenic metabolism, (b) autolysis of liver cells; (4) some regard the condition as a form of diabetes mellitus in which the pigmentation is an incidental and secondary occurrence; and (5) many workers believe that there

may be a concomitant pigmentation and cirrhosis of the pancreas. These we will discuss in order.

Primary blood destruction or intravascular alteration of hæmoglobin with the production of pigment deposits as the basis for the sequence of events in the disease was first discussed by von Recklinghausen in 1889. He described hæmofuscin as a pale yellow non-iron-containing pigment in smooth muscle cells of stomach, intestine, blood vessels and lymphatics, and occasionally in the bladder, ureter and vas deferens. He also noted it in the connective tissue cells of Glisson's capsule, splenic trabeculæ, adrenal and the sheaths of blood vessels. In the twelve cases studied by von Recklinghausen a local and general pigmentation of the organs were observed. To this pathological condition he gave the name, hæmochromatosis. He claimed that the pigment was derived from the blood.

Processes of active blood destruction have been found in the majority of the cases of hæmochromatosis. Hæmorrhage was noted in some. Purpura was reported in four cases by Opie and recurrent purpura was observed in a case by Anschutz. Hindenlang described a case associated with morbus masulous Werlhoffi. Hintz reported two cases having hæmorrhagic pericarditis and peritonitis and one case with subcutaneous hæmorrhages. Quincke and Tillmans have reported large extravasations of blood in various tissues. Buss reported cases with hæmorrhagic pleurisy, peritonitis and pachymeningitis. Abbott and Hintz have noted chronic intestinal disease. Potter and Milne observed the presence of tuberculosis and sepsis. Sprunt had two cases with a history of dysentery. Malaria has been noted by Osler and Rolleston. Skin lesions with focal hæmorrhages have also been frequently described. Futcher had one case having a papulo-squamous eruption over the legs and one with a red eruption over the chest a week before death. Osler noted purpura and urticaria over the legs in one case and erythma nodosum in the other. Parker's case had a chronic varicose ulceration of the leg.

Anæmia was described in a case showing widespread pigmentation in the liver, spleen, and pancreas by Quincke. However, this is the only case in which a true anæmia has been described. Sprunt says in his cases the average of four counts in three cases was 4,709,000 red cells and hæmoglobin of 90 per cent. Jeanselme reported a count of 3,379,000 and later 3,308,000 red cells shortly before death, but did not see any nucleated cells. Futcher in two cases reported counts of 4,800,000 and 5,304,000 red blood

cells and hæmoglobin 87 and 95 per cent. respectively. Osler's case showed an increase in red blood cells. Ridder's case showed 4,400,000 red blood cells as the lowest count. Differential counts of the white cells have always been normal. Lipæmia has been noted. No unusual blood cells have been reported by any of the authors.

Potter and Milne suggest that an excessive blood destruction must have occurred in some cases as the accumulation of pigment was enormous and occurred within a short period of time. They note, however, that generally speaking the destruction of blood must be slow to permit a more or less complete regeneration as indicated in high blood counts commonly found.

M. E. Abbott who studied the only complete case of hæmochromatosis reported in a woman, believed that simple blood destruction in itself did not cause hæmochromatosis, but that another factor such as degeneration of cells of certain organs whereby they were unable to throw off the pigment reaching them, must be associated with it. She believed that with the disintegration of these cells the liberated pigment induced an interstitial inflammation and cirrhosis of these organs. The whole process was supposed to have some active cause leading alike to blood destruction and cell degeneration, such as a bacterial infection with chronic suppuration or chronic intestinal disturbance. Adami believed that a true destruction of red blood cells occurs over a long period of time and also suggests that it is the result of bacterial invasion. Abbott believed that the pigment formation occurred before the cirrhosis, because evidences of broken down heavily pigmented liver cells lying in new formed connective tissue areas were found. Opie, Anschutz, Hintz, and Kretz have all made similar observations and draw the same conclusions. Abbott studied forty-one other cases in which a golden brown pigment could be demonstrated microscopically in the liver cells. Cases of pernicious anæmia were not included in this series. In four of these cases the presence of hæmosiderin was demonstrated. A history of localized blood disintegration or some chronic intestinal disturbance was revealed in all. Abbott also suggested that both hæmosiderin and hæmofuscin contain iron.

In his conclusions on a series of twenty-four cases Anschutz particularly brought out the fact that the blood destruction and the blood formation did not keep pace with each other, with the result of enormous deposits of pigment in the tissues. At the same time he noted a diseased condition of the glandular organs, which

under some mysterious influence took up and bound large amounts of the products of blood destruction. In the organs in which evidence of degeneration was more pronounced, a reactive inflammation resulted in connective tissue growth. Diabetes, he claimed, is the result of these extensive lesions involving the pancreas.

Rossle held that the blood destruction was secondary to capillaritis with hæmorrhage and that the abnormal hæmolytic and phagocytic activity of the liver cells accounted for the marked pigmentation of that organ. Pigment, resulting from destruction of red blood cells in liver cells, was later disseminated by the blood stream through the whole body. He believed that after this stage there is rapid regeneration of blood. Potter and Milne substantiate the finding of phagocytosis of red cells by the liver cells under pathological conditions, but, at the same time, believe that these liver cells are degenerated. They ask why should spontaneous phagocytic activity on the part of liver cells for red blood cells alone occur and if this is the cause of hæmachromatosis, why is the condition so rarely seen clinically.

Marie believed that there was some primary cause for the dissolution of hæmaglobin in the blood and tissues as shown by the presence of pigment in the various body cells. He advanced the idea that this pigment in the cells was laid down by the cell as a protection against the irritating substance destroying the hæmoglobin. This pigment in turn causes degeneration and destruction of these cells with supplementary elimination by way of lymphatics and overloading of the lymph nodes and production of inflammation and fibrosis. He concluded that bronzed diabetes was neither an ordinary clinical nor pathological diabetes, but rather a clinical entity in itself.

Achard, Dutournier and Jeanselme reiterate the statements of Marie, and as expressed by Futcher, they presuppose an unknown type of blood destruction. Opie expresses the opinion that under the conditions of the disease there is an active hæmolytic and toxic substance in the blood which transforms hæmoglobin into hæmosiderin. Buss studied one case and come to the conclusion that primary blood dissolution was the ætiological factor of the fibrosis and diabetes.

Hunter in 1888 was the first to contest blood destruction as primary in the process. He showed that hæmorrhage into the skin would only cause a local deposit of iron-containing pigment and no accumulation elsewhere. Cases of epistaxis and chronic suppuration were studied by Abbott and a case of purpura by Zaleski,

without finding any deposit of iron pigment. Futcher did not find any pigment deposit in a case of purpura and Hiss and Zurhelle had similar negative findings in a case of hæmoglobinuria.

Kretz studied cirrhosis of the liver and in fourteen of twenty-six cases he found there was hæmosiderin in the liver. He concluded that the same toxic substance caused degeneration of the liver cells and injured the red blood cells. Abbott also found hæmosiderin in six out of sixteen cases of cirrhosis of the liver and concluded that the two factors, liver disease and blood cell destruction were essential. She noted œsophageal hæmorrhage and other hæmorrhages in these cases of cirrhosis. However, Marie regarded the tendency to hæmorrhage in hæmochromatosis as a secondary manifestation. Potter and Milne believed that these hæmorrhages found in hæmochromatosis were no more than those seen in any ordinary cirrhosis of the liver. Anæmia is usually slight or absent and evidence of blood destruction was not found by them.

Sprunt noted that the pigment deposit varying considerably in quantity, exceeded that in pernicious anæmia. He further observed that the bone marrow was not actively hæmopœtic and in the study of three cases but one showed slight hyperplasia. He concluded that the findings were insufficient to signify blood destruction since in hæmochromatosis other pigments are found having no relation to hæmoglobin. Elmer studied hæmochromatosis and found no anæmia, hæmolysis nor hyperplastic bone-marrow.

French found no free pigment in the blood, but all of it was intracellular, and on this account concluded that the pigment formation did not occur in the blood stream but in the living cells.

Experiments have rather proved against an abnormal blood destruction as the primary cause of hæmosiderosis. Auscher and Lapique injected blood into the peritoneal cavity and found iron pigment in the spleen but not in the liver. He considered that he had produced hæmochromatosis but no connective tissue increase or inflammatory reaction in the tissues. Biondi gave toluylendiamin by mouth and subcutaneously to produce blood destruction. He produced anæmia, jaundice, hæmoglobinuria, pigmentation of liver, spleen, bone-marrow, lymph nodes and occasionally kidney. His conclusions were that this hæmoglobinæmia which he had produced caused the liver cells to increase their secretion of bile, even to such an extent as to cause jaundice without obstruction of the bile passages. The other part of the hæmoglobin molecule,

the iron-containing one, was taken up by leucocytes and distributed to other organs. He only found hæmosiderin in degenerated liver cells, and inferred that the diseased liver cells lost their normal capacity of ridding themselves of iron-containing pigment and that siderosis was but the expression of this fact. Sprunt discussed this experiment and concluded as there was no cirrhosis that it had no bearing upon the case in point.

Rolleston suggested that since in chronic hæmolytic jaundice there is destruction of red blood cells, the absence of jaundice in hæmochromatosis would argue against the existence of active hæmolysis.

The theory that the pigment under discussion is produced in the various parenchymatous cells or by some chemical change in the chromogenic constituents of cells was advanced by Mosse in 1894. He held that pigment was formed universally, even in the deeper cells of the Malpighian layer of the skin and was not transferred from other places of formation. The pigment accumulation in the liver is in proportion to the specialization of these cells to the chromogenic function and to the volume of blood which transverses it. He also believed that hyperglycæmia altered the blood before this specialization. On the other hand Macallum stated that iron is found in all nuclei in amounts proportionate to the chromatin present in the cytoplasm of all gland cells producing ferments. Opie suggested that the same condition which causes the deposit of pigment favours chromogenic metabolism, especially in the liver, which is present under normal conditions. This chromogenic metabolism may be the cause of pigment deposits in other organs, or it may be that the iron-containing derivatives of hæmoglobin are not eliminated by the liver and are left in the blood.

Parker believed that there was no unusual blood destruction but that there was an accumulation and lack of elimination of the normal end products. The hæmoglobin lies where it falls and undergoes some chemical change. He concludes that some toxic agent causes degeneration and chronic inflammatory changes in the liver and pancreas. Heller and Martineck are of the same opinion. Parker refers to Croftan's experiments and states that when the pancreatic lesion is of sufficient intensity there is insufficient glycolytic ferment produced by the islands of Langerhans, to act with the muscle ferment in the oxidation processes of carbohydrate metabolism. The glycogen then is not stored and a hyperglycæmia results, which in turn, causes the changes of hæmoglobin into hæmosiderin, instead of bile pigment. He also pointed out

that if the liver be normal the pigment is removed and the case is one of frank diabetes, whereas if the liver is cirrhotic the pigment is not eliminated and accumulates with hæmochromatosis as an end result.

Recently Garrod, Gaskell, Sladden, Wallis and Vaile together have reported a case in which they favour the idea of defective elimination because they did not find iron in the bile, fæces, or urine. They found that there was an increased amount of iron in the blood (from 0·042 to 0·048 and 0·056 per cent.). They proved pancreatic insufficiency the cause of the diabetes. Of note is that they also found hæmosiderin in the distal convoluted and collecting tubular renal epithelium in bronzed diabetes and in the proximal convoluted tubules in pernicious anæmia. They brought out the old theory of resorption of certain substances by the collecting tubules, in explanation of hæmosiderosis in bronzed diabetes as a result of defective elimination.

Brown attempted to prove that the process of pigmentation is not hæmolysis but autolysis. He placed rabbit's liver in moist aseptic chambers and incubated at 37°C. The results of his experiments showed an increase in the iron-containing pigment near the exposed or outer surfaces, and from this he concluded that hæmosiderin was the oxidation product of hæmoglobin due to enzyme action. Along these lines Sprunt suggested a widespread parenchymatous degeneration of a specific nature affecting many organs and leading to the deposit of a variety of pigments depending upon the chemical process in the cells. Moreover, he found little justification for the theory of primary blood dyscrasia since no anæmia was present and the bone marrow was negative. The pigment also exceeds that found in pernicious anæmia and he holds that it is a different chemical nature. He concludes that hæmochromatosis is a metabolic disease implicating many tissues and manifested by changes in the chromogenic groups or protein molecules of cells with the deposit of pigment. As a result of pigment accumulation in the interstitial tissues there occurs a reactive inflammation with fibrosis in various organs.

Sprunt, Colwell and Hagan supporting the theory of autolysis and following Brown's experiment placed sections of the perfused liver of a rabbit into aseptic moist chambers and incubated at 37°C., while others were exposed to sunlight. They did not get constant results. From their observations they have shown that iron-containing and other pigments may be found during autolysis of the parenchyma independent of hæmoglobin and hence are

derived from the protein constituents of cells. Gortner has demonstrated that the pigmentation of the integuments of larva to be the result of the interaction of oxydase and chromogen. The chromogen is present in very small quantities and is probably secreted only as needed for pigmentation while oxydase is present in relatively large amounts. The pigmentation produced by autolysis can, therefore, be explained by the action of oxydases on the chromogenic radical of the protein molecule. It is known that excessive chromogenic material is present in peculiar degenerations of the cell protoplasm and when acted upon by the ever present oxydase is precipitated a pigment.

Hess and Zurhelle believed that increased blood destruction is not necessary but that the abnormal retention of pigment is sufficient to explain this condition. They estimated 38·7 gm. of iron in the liver of their case which is one hundred times that of normal liver, fifteen times that of hæmoglobin and ten times that of the whole body; and in the pancreas, heart, and lymph nodes, 12 gm., totalling about 50 gm. in the body. They estimated the whole amount in normal blood at 2·4 gm. Since about one tenth of the red blood cells are dissolved in one day thus liberating 0·24 gm. iron and if little were lost by excretion it would require about seven months to produce the amount found in their case. This would be a very short time for this disease to develop.

Similar large amounts of iron have been isolated from the liver by Anschutz, Muir, and Dunn. The latter authors estimate that the total quantity in the body in bronzed diabetes is well over 40 gm., while under normal conditions there is not over 5 gm. They point out that the food is the ultimate source of the iron of the body and that the daily intake cannot be more than 30 mgm. If the source of the iron deposits were alone from the food, it would take some three years to accumulate the quantity found in the tissues in bronzed diabetes. As Garrod was unable to find any iron in the urine, bile, or fæces in bronzed diabetes, it would appear that there was an unusual retention of these substances by the tissues. In marked contrast are the results of iron deposit in pernicious anæmia where the various excreta contain iron bearing subtances, while the remaining surplus accumulates in the tissue. Under experimental conditions this tissue accumulation is only transient in that with the removal of the blood destruction the pigment substances soon leave the tissues. There is much to be said for the contention that bronzed diabetes is in great part determined through an unusual iron retention of the tissues. Muir and Dunn

suggest that many tissues have an unusual affinity for iron in this disease.

In a subsequent series of experiments the authors demonstrated that iron is rapidly stored in the liver and other organs during an experimental anæmia. The iron in the liver and kidneys is, under these conditions, increased five fold and in the spleen three fold. Nearly all the iron attending the destruction of blood accumulates in the liver, spleen, and kidneys. A relatively small amount escapes in the urine. It was further found that the iron stored in various organs again disappears with the regeneration of blood and probably has been utilized in the process of blood formation.

Since Hanot's report in 1882, most of the French authors have held that diabetes was the primary condition leading to blood alteration and destruction. In 1882 Hanot and Chauffard found that pigment hypergenesis of the liver cells was due to nutritional disturbance brought on by an associated diabetic endarteritis. They believed that the pigment was distributed from the liver as emboli. Letulle suggested hyperglycæmia as the cause of the blood destruction and said that the pigment was formed everywhere and accumulated in situ, especially in dead liver cells. He discredited Hanot's idea of hypergenesis particularly as he noted degeneration and pigmentation of heart cells. This observation led him also to believe that the embolic theory of Hanot's was not tenable. Brault and Galliard laid stress on diabetes as the etiological factor in the pigmentation because it seemed that in this disease the hæmoglobin is rendered incapable of transformation into normal bile pigments. They considered diabetes and liver cirrhosis concomitant, in which the degenerated liver cannot elaborate and utilize the altered blood pigments. Hernandez thought that the dissolution of hæmoglobin was due to the diabetes and that the pigments deposited in the cells of the liver altered their nutrition and finally caused their destruction. He held that the pigment could be carried by the lymphatics. Mosse believed that hyperglycæmia caused the dissolution of hæmoglobin and that the pigment deposit in the liver was in proportion to the specialization of the chromogenic function of liver cells and also to the volume of blood passing through the organ. De Massary and Potier confirm this.

Rendu and de Massary advance the hypothesis that pigment is deposited in various cells by the abnormal action of tissues on the hæmoglobin. This altered metabolism is but the manifestation of a general cachexia caused by diabetes associated with cirrhosis of the liver. Naunyn ascribed the diabetes in some cases of hæmo-

chromatosis to cirrhosis of the liver. Potter and Milne claim that in 2 per cent. of cirrhosis of the liver there is diabetes while Palma and Van Noorden hold diabetes and cirrhosis so rarely concomitant that it is only a coincidence. Simmonds reports cirrhosis of the liver in 5 per cent. of diabetes. Futcher noted bronzing in 2 per cent. of 256 cases of diabetes.

Buss found that glycæmia may result in incomplete oxidation of altered hæmoglobin. Parker has questioned the relation of diabetes to pigmentation. In ordinary diabetes there is no accumulation of iron pigment as indicated in the studies of Zaleski, Kretz, Hanot, and Hanseman.

Another group consisting mostly of German authors have considered cirrhosis of the liver and diabetes concomitant but that the diabetes comes on when interstitial fibrosis of the pancreas has reached an advanced stage. This view based upon the clinical finding of diabetes as a terminal condition is at present held by most authors. The diabetes is often very severe after the patient has shown pigmentation of the skin. The patient usually lives but a year or a little more and dies in diabetic coma.

The true sequence of events as believed by Marie, Acard, Dutournier, Jeanselme, Anschutz, and Opie is that blood destruction or altered chromogenic function with or without concomitant degeneration of liver and pancreas, or with subsequent interstitial inflammation and fibrosis of the liver and pancreas, is the first stage of the disease or simple hæmochromatosis, and that when the chronic intra-acinar pancreatitis has reached a sufficient degree of severity the characteristic symptoms of diabetes develop. Potter and Milne hold that in every case of liver cirrhosis hæmosiderin may be found in some of the organs and that hæmochromatosis is but an exaggeration of this. The cirrhosis is primary and is the result of the same toxic agent which produces the blood destruction. The pancreas may be damaged as a sequel to or coincident with the cirrhosis of the liver, or on the other hand, it may be due to a catarrhal inflammation of the secretory channels of pancreas with secondary atrophy and sclerosis.

In our own case no blood counts were recorded which would indicate the degree of blood destruction, but the patient was observed to be quite anæmic for a long time. He had, however, never had any gross hæmorrhage. One point of note is that our patient had been a plumber the greater part of his life and might have suffered, although never recognized, lead poisoning with its associated blood destruction.

We consider blood destruction to some degree a factor in the production of hæmochromatosis, pointing out that blood counts had only been taken during the later stages of the disease in other reports. I have noted in a case of primary carcinoma and cirrhosis of the liver as well as in several cases of pernicious anæmia a considerable pigmentation of the liver and spleen. The distribution of pigment in these cases is both in Kupffer's cells and liver cells, but in considerably smaller amounts than in bronzed diabetes. I have also noted in a case, twice having chronic lead poisoning, an iron-containing pigment in the Kupffer and parenchyma cells of liver. Ophuls in his reports on chronic nephritis by lead poisoning has likewise noted pigment deposits. A case of advanced tuberculosis with marked anæmia reported by Roque, Chalier, and Josserand showed pigment deposits especially in the liver and spleen, an advanced stage of hæmochromatosis.

The small amount of iron-containing pigment in the kidney was remarkable in comparison to the deposit found in other organs. In our analysis of tissues in pernicious anæmia a much larger quantity was found in the kidney. These results are parallel to the urinary findings, where no particular pigment is observed in bronzed diabetes while a varying and even marked amount may be observed in pernicious anæmia. The difference suggests the lack of a mobile pigment in the former. It is of interest, however, that whereas in bronzed diabetes the pigment deposit in the kidney is localized to a few cells, that in the anæmias the deposits may occupy various portions of the tubules. The presence of iron-containing pigment in the fæces, in view of the liver cirrhosis and the associated portal stasis and hæmorrhage, has no renal significance.

The experiments of Auscher and Lapique, Meunier and Biondi, have shown that blood destruction caused a deposit of iron-containing pigment in varying amounts. These experiments show that some added factor must be necessary to produce fibrosis. Time may be that factor because the portal cirrhosis of the liver in bronzed diabetes is of long duration, while the experiments and the course of pernicious anæmia are usually more acute. Alcoholism or lead poisoning may also be an associated exciting factor.

In our case, pigment deposits as well as sclerosis were found in large amounts in the liver, pancreas, lymph glands about the pancreas, spleen, heart, thyroid, and adrenal. It is possible that it was present in more tissues. Others have found iron-containing pigment in Brunner's and the glands of stomach, duodenum, and

small intestine. Likewise pigment has been found in the parathyroids and the glands about the trachea, bronchi, and larynx as well as in the skin, œsophagus, aorta, submaxillary, axillary, mesentery, and mediastinal glands, in cartilage cells of trachea and costal cartilages, in the kidneys, bone marrow, and in several cases in the testes, prostate, vas deferens, seminal vesicles, and urethral epithelium.

In the case reported, definite pigmentation of the skin was not noted at autopsy, but a slight and varying pigmentation of the exposed surfaces was noted clinically. The skin pigmentation is the not uncommon clinical feature of the disease by which it is recognized during life. When present it is most marked on the exposed parts, the face, neck, back of hands, shins, in the axilla and groin and about old scars and is of a diffuse slaty blue or brownish gray colour with darker spots like freckles. No pigment is seen in the sclera or on the mucous membranes.

The distribution of the iron pigment in cells is not regular. Side by side one collection of cells may be filled with granules, while others nearby may show little or none. There is commonly no relation between the pigmented cells and the blood or lymph channels. It has been suggested that the pigment accumulates in the cells on account of an abnormal condition under which they are placed, and that cells which normally have no relation to pigment production are found to deal with this unusual product.

Of the chromogenic metabolism of cells we know but little. The accumulation of blood derivatives might result from the hæmoglobin reducing processes of the liver and heart, but this would hardly suffice to indicate the mode of deposit in the lining cells of the thyroid and pancreas. There can hardly be any doubt that there is some alteration in the chemistry or selective activities of the various cells whereby they show an abnormal property of taking up iron pigment. Whether the excretory organs themselves have an unusual ability of withholding iron from their secretions is not clear.

The pigment is not only distributed to glandular cells, but also to connective tissue, endothelial and lymphatic cells. These cells obtain their pigment directly from the blood as is indicated in the widespread and irregular distribution with no relationship to other structures. Free hæmoglobin has not been demonstrated in any of the reported cases, but this may be the result of faulty technique. The chemical tests for minute quantities of iron-

containing pigment in the blood plasma are insecure, and spectroscopic methods have as yet not been applied in these cases.

Another point of contention and cause of much discussion is the finding of the two pigments, hæmofuscin and hæmosiderin, in almost all the organs. These pigments have commonly been found side by side and have about the same morphology, the hæmofuscin being of a canary yellow, while hæmosiderin is rusty brown and usually in large coarse clusters. Many authors have used some modification of Perls' reaction, obtaining better results with the hot hydrochloric acid as suggested by Abbott. In our case the pigment did not react to the original Perls' test but showed a slight reaction when the hot hydrochloric was used. On the other hand a brilliant reaction was obtained by Nishimura's ammonium sulphide modification of Perls. It would appear from our results that possibly all of the pigment is iron-containing, but some is more closely bound and hence more difficult to demonstrate. A similar view has been expressed by Abbott, Futcher, Hiss and Zurhelle, Sprunt, and others. M. B. Schmidt points out that although the pigment fails to respond to the available tests for iron, it is not necessarily iron free and hæmofuscin may be an older stage in the chemistry of the pigment.

In our case cirrhosis of the liver was not recognized during life, the liver being slightly enlarged and there being no ascites. The spleen showed no enlargement. There were no hæmorrhages. However, there had been a long period of dyspeptic symptoms with tenderness in epigastrium, which in the absence of any lesion in the stomach and intestines may have had some association with the cirrhotic liver. The fibrosis of the liver is probably not directly due to the pigment deposited in interstices by degenerating cells. as it is not disposed around the pigment masses. This can be said only in part of the other organs because some show evidence of irritation and an enclosing fibrosis. Particularly was this true of the lymph glands.

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THE AMERICAN ASSOCIATION OF

Pathologists and Bacteriologists

PROGRAM

OF THE

Eighteenth Annual Meeting

PHILADELPHIA

MARCH TWENTY-NINTH AND THIRTIETH

1918

The Meetings of the Association will be held in the Laboratory of Hygiene, University of Pennsylvania, 34th Street between Walnut and Spruce.

In accordance with the custom of the Association the time limit will be strictly observed and the discussion of each paper will be limited to five minutes. The order on the program will be adhered to.

The Headquarters of the Association will be at the Bellevue-Stratford Hotel. After March twenty-seventh and during the meeting the address of the Secretary will be at the Bellevue-Stratford Hotel.

The American Section of the International Association of Medical Museums has postponed the holding of its annual meeting.

The Ameriean Association for Cancer Research will hold its meeting on March twenty-eighth at the University of Pennsylvania.

The American Association of Immunologists will hold its meetings on the mornings of March twenty-ninth and thirtieth. It will meet with the American Association of Pathologists and Bacteriologists on the afternoon of March twenty-ninth.

FRIDAY, MARCH TWENTY-NINTH

MORNING

The Association will meet at the Laboratory of Hygiene, University of Pennsylvania, at nine-thirty o'clock.

1. Report of the Council and election of officers.

2. Anna W. Williams of New York. Studies on meningococcus carriers.

3. J. Bronfenbrenner and M. J. Schlesinger of Boston. A simple method of carrying meningococcus cultures.

4. W. L. Holman of Pittsburgh. The value of a cooked meat medium for routine and special bacteriology.

5. Aaron Arkin of Morgantown. The influence of an oxidizing agent (sodium iodoxybenzoate) on the catalase value of the blood and tissues.

6. S. R. Haythorn of Pittsburgh. Experimental trinitro-toluene poisoning.

7. Wm. de B. Macnider of Chapel Hill, N. C. A study of acute bichloride intoxication in the dog (with lantern demonstration).

8. E. T. Bell and W. P. Larson of Minneapolis. The effect of foreign protein on the kidneys.

9. R. A. Johnson and E. T. Bell of Minneapolis. Functional studies on experimental hydronephrosis.

10. Harry T. Marshall of University, Va. A case of chronic pseudo-leukaemia.

11. H. T. Karsner of Cleveland. Autopsy service of a Military Hospital.

12. Herbert W. Williams and Harold A. Patterson of Buffalo. Observations on haemagglutination.

The members of the American Association of Pathologists and Bacteriologists are invited, as the guests of the Pathological Society of Philadelphia, to a buffet-luncheon at Houston Hall, University of Pennsylvania.

FRIDAY, MARCH TWENTY-NINTH

AFTERNOON

The Association will meet at two-thirty o'clock in the Laboratory of Hygiene, University of Pennsylvania, conjointly with the American Association of Immunologists.

1. Ralph R. Mellon of Rochester. A contribution to the bacteriology of B. fusiformis; its morphologic phases and their significance.

2. G. Benjamin White of New York. The various immunological reactions in glanders (with lantern demonstration).

3. Wm. H. Park of New York. Persistence of active immunity in those immunized against diphtheria.

4. John G. Wurtz and S. W. Sappington. A simple method for blood cultures.

5. Miriam P. Olmstead. A bacteriological study of post operative pneumonia.

6. R. Kohn of Boston. The active immunization against pneumonia.

7. G. Benjamin White of New York. Production pneumococcus anti-serum and the corresponding curves obtained by protection and agglutination tests.

8. Chas. Krumwiede, Jr. of New York. A rapid simple method for the determination of type of pneumococcus in the sputum of lobar pneumonia.

9. John A. Kolmer, Edward Steinfield and Charles Weiss of Philadelphia. Experiments upon the chemotherapy and chemoserotherapy of pneumococcus infection.

10. John A. Kolmer, Charles Weiss and Edward Steinfield of Philadelphia. Studies on the toxicity of pneumonic lungs.

11. Charles Weiss and John A. Kolmer of Philadelphia. The properties of pneumotoxin and its probable role in the pathology of lobar pneumonia.

12. C. S. Allison of Pittsburgh. (Presented by S. R. Haythorn). Observations on the use of salvarsan in acute infection.

FRIDAY, MARCH TWENTY-NINTH

EVENING

Seven-thirty P.M. The Annual Dinner. An announcement will be made on the morning of the first day concerning the arrangements for the dinner.

SATURDAY, MARCH THIRTIETH

MORNING

The Association will meet at the Laboratory of Hygiene of the University of Pennsylvania at nine-thirty o'clock.

1. H. G. Weiskotten of Syracuse. The action of bezol. Benzol atmosphere leucopenia (rabbit) (with lantern demonstration).

2. H. G. Weiskotten and H. S. Steensland of Syracuse. The action of benzol aplasia of thymus (rabbit).

3. Alfred F. Hess of New York. Focal degeneration of the lumbar cord in a case of infantile scurvy (with lantern demonstration).

4. J. C. Torrey and Alfred F. Hess of New York. Intestinal flora in scurvy of guinea pigs and of infants.

5. J. Bronfenbrenner of Boston. On methods of isolation and identification of bacteria of the colon-typhoid group.

6. W. L. Holman of Pittsburgh. Some fundamental studies on the grouping of anaerobes.

7. S. A. Goldberg of Ithaca (by invitation). Certain structural changes in subacute and chronic arthritis of horses and cattle (with lantern demonstration).

8. Leo Loeb of St. Louis. Grafting of tissues into members of the same family.

9. Leo Loeb of St. Louis. Immunity against grafted tissues.

10. W. P. Larson and O. McDaniel of Minneapolis. The effect of carbon dioxide under pressure upon bacteria and filterable viruses.

11. Paul A. O'Leary and A. H. Sanford of Rochester, Minn. Phialophora verrucosa (Thaxter). Report of case of chronic cutaneous infection in which an unusual hyphomycete was isolated from the lesion (with lantern demonstration].

12. De Wayne G. Richey of Pittsburgh (by invitation). Bacteriemias in the agonal period.

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